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Review article

Is surface modification effective to prevent periprosthetic joint infection? A systematic review of preclinical and clinical studies

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ABSTRACT

Background: With increasing recognition of the importance of biofilm formation in the pathogenesis of periprosthetic joint infection (PJI), a push towards finding solutions to prevent PJI via surface modification of prostheses is occurring. Unlike the promising in vitro antimicrobial effects of these surface modifications, the preclinical and clinical prophylactic effects vary and are debated. Therefore, we performed this systematic review to answer: (1) what kinds of methods of surface modification are used in preclinical and clinical studies to prevent PJI, (2) whether these modifications are effective to prevent PJI.
Methods: Electronic searches were performed using PubMed, Embase and the Cochrane library databases up to and including December 2017 with predetermined criteria: (1) in vivo studies with (2) surface modification for prophylactic effects against infection. Both animal studies and clinical trials were included. Data were extracted and presented systematically.
Results: Overall, 21 studies were included. Among these, fourteen were carried out in animal models and seven were clinical studies. In the animal studies, six used antibiotics and six silver modifications, while copper and Cationic Steroidal Antimicrobial-13 were each used for one study. In the seven clinical studies targeting patients with high infection risk, five of them focused on silver-coated prostheses and the remaining two studied iodine-coated implants. In all of the animal studies, when compared with the control group, the surface modified groups had a lower infection risk (RR ranging from 0 to 0.71). Clinical studies using silver-coated prostheses also demonstrated a lower infection risk (RR ranging from 0.24 to 0.70), while iodine-coated implants showed a 0% and 5% incidence of PJI in the two case series included.
Discussion: The results from the publications included in this review indicate that surface modification, especially antibiotic and silver modifications, are helpful preventing PJI in both preclinical animal models and in clinical trials.
Level of evidence: III, systematic review of level III retrospective comparative studies and level IV case series and animal experiments.

1. Introduction

Periprosthetic joint infection (PJI) is a major complication after joint arthroplasty, which accounts 11.4%–14.8% of hip revision procedures and 11.3%–25.2% of knee revision surgeries [1–3]. Longer hospital stays, higher costs, and higher morbidity and mortality have been reported when compared with primary joint replacement procedures [4–7]. As reported, PJI has resulted in nearly $1 billion financial burden in the USA in 2015 [8]. Conventional prevention protocols for PJI include sterilization, prophylactic antibiotics and monitoring operating room traffic, among others [9–11]. However, the incidence of PJI after joint replacement continues to persist in 1% to 2% of cases and is even higher in patients with increased risk [12–15].

Biofilm, formed by the bacteria or fungi, has proven critical in PJI [16,17]. As the place where biofilm forms, the surface of the implant has been suggested as a point of modification in an effort to promote an antimicrobial environment. In this regard, different modifications have been proposed and tested to prevent PJI, such as antibiotic or silver surface modification [18]. Given that most studies were done in vitro, prophylactic effects against infection in both animal models and patients of these surface modifications remains a subject of debate. Silver coating has showed promising results according to Akiyama et al. [19] and Qin et al. [20], while no significant difference in the incidence of PJI was reported by Hardes et al. [21]. To the best of our knowledge, no systematic

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review has been published regarding the preclinical and clinical evidence detailing prophylactic effects against PJI encompassing these surface modifications.

Therefore, we performed this systematic review to answer:

- what kinds of methods of surface modification are used in preclinical and clinical studies to prevent PJI;
- whether these modifications are effective to prevent PJI.

2. Material and Methods

2.1. Search Strategy

This study was registered in the international prospective register of systematic reviews (PROSPERO) (CRD42018102468). The systemic review was performed using the method described by the Cochrane Handbook and the PRISMA checklist guidelines [22,23].

We searched the eligible studies from PubMed, Embase and Cochrane library up to and including December 2017. The terms used in the search process are outlined in Table 1. After the screening process, the bibliography of the included articles and any relevant reviews were also checked to identify possible studies for inclusion in this review.

2.2. Eligibility criteria

To identify the appropriate articles relevant to the purpose of this study, the following inclusion and exclusion criteria were outlined before screening process began. The including criteria were:

- in vivo studies (animal studies and clinical studies);
- modification of a prosthetic surface for prophylactic effects against infection.

Any modification, by any biologic, chemical or physical methods, were included. We excluded studies relating to the deposit of the antibiotics directly on the surface of the implant, or those using cement or gel to carry the antibiotics. Case reports and reviews were also excluded, as were conference posters or abstracts.

2.3. Study selection and data extraction

Two orthopedic surgeons independently reviewed the titles and abstracts to screen for eligibility. If any inconsistent results occurred, a third senior orthopedic surgeon was utilized for consensus.

Once we determined the final list of included studies, standardized forms were used to extract the data. For animal studies, information of publication, animal models, used implants and bacteria, outcomes measurements and results were extracted. For clinical studies, information of publication, patient characteristics and indications, used implants, surface modification and clinical outcomes were extracted. If the information could not be extracted from the original paper, we contacted the corresponding author to request specific details.

Table 1
Terms for the search strategy.

Search Strategy	
Database	Embase, PubMed and Cochrane library
Strategy	#1 AND #2 AND #3 AND #4 AND #5AND#6
Time	Until December 31st, 2017
#1	bacteria OR bacterium OR adhesion OR biofilm OR infection OR antimicrobial OR antibacterial OR "bacteria killing" OR decontamination
#2	implant OR implants OR prosthesis OR prostheses
#3	"surface modification" OR "modified surface" OR coating OR coated OR functionalization OR functionalized OR "chemical modification"
#4	(arthroplasty OR replacement) AND (joint OR hip OR knee)
#5	"in vivo" OR animal OR human
#6	English [Language]

2.4. Quality assessment

Two reviewers assessed independently the quality of the included studies. As a result of the different types of studies included, we used SYRCLE's RoB tool for animal experiments, the Newcastle-Ottawa Scale for retrospective cohort studies, as well a checklist published by the Institute of Health Economics (IHE) of Canada for case series [24–27]. If disagreement regarding the bias occurred, a final assessment was made by the third, senior orthopedic surgeon.

2.5. Statistical analysis

Review Manager (version 5.3 from Cochrane Collaboration) was used to perform the statistical analysis. Only descriptive statistics are reported and we calculated risk ratios (RR) for dichotomous data.

3. Results

3.1. Study selection and characteristics

There were 605 studies identified from the initial search. After evaluation of the titles and abstracts, we excluded 579 studies and reviewed the full texts of the remaining 26 studies. Eleven studies were excluded based on the full text review. After reviewing the fifteen remaining studies and their bibliographies, an additional six studies identified in the reference lists met the inclusion criteria. As a result, there were 21 articles included in this systematic review (Fig. 1).

Among the 21 studies included, fourteen were animal studies and the other seven were clinical studies. In the fourteen animal studies (Table 2), six used modifications with antibiotics for prevention of periprosthetic infection [28–33], six focused on silver modification [19,20,34–37], one study utilized copper and another investigated Cationic Steroidal Antimicrobial-13 (CSA13) [38,39]. The characteristics of these studies are included in Table 2. In the seven clinical studies, which all targeted patients with high PJI risk [21,40–45], five used a silver-coated prosthesis to prevent infection and two case series report using iodine modified implants. The details of clinical studies are presented in Table 3.

3.2. Quality assessment

The SYRCLE's RoB tool was used to assess the quality of the animal studies included, which demonstrated low quality of the included studies (Electronic annex 1). With the Newcastle-Ottawa Scale for clinical comparative studies (Electronic annex 2) and the checklist from IHE for the assessment of clinical case series (Electronic annex 3), the quality of the included clinical studies was deemed as not high.

3.3. Animal studies

In the six studies using antibiotic modification, three rat or mouse models and three rabbit models were used. Three studies reported a lower infection rate with risk ratios (RR)

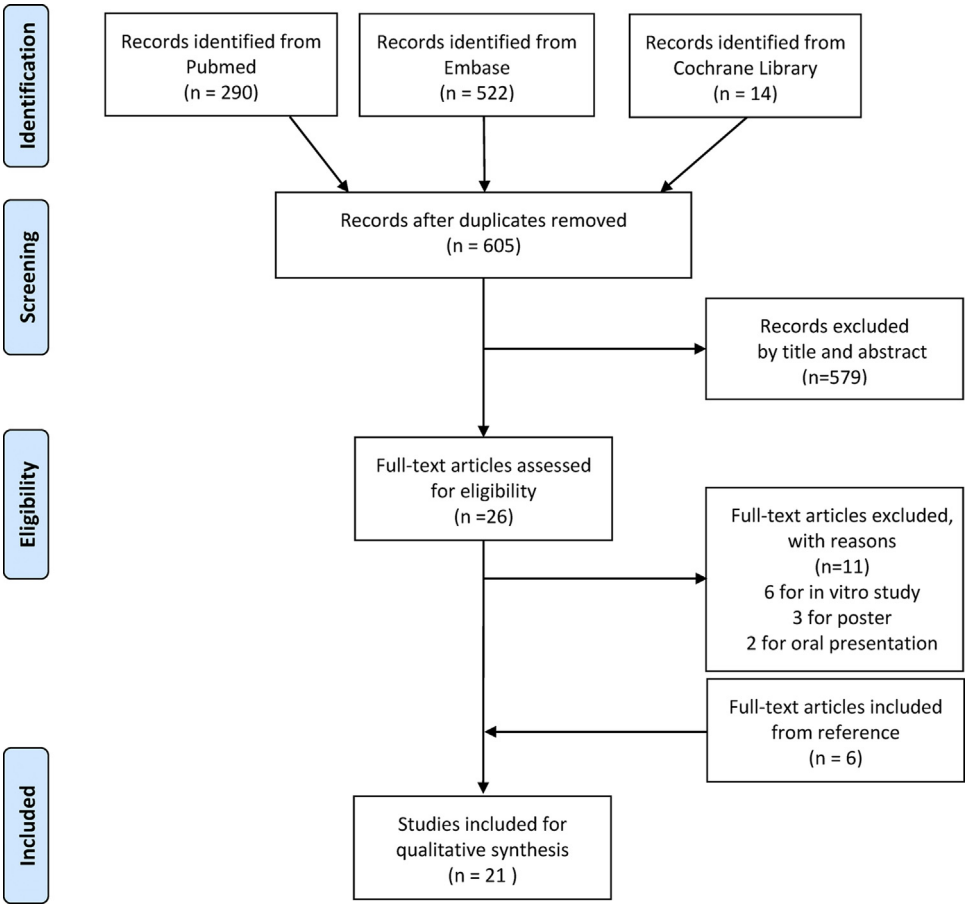

Fig. 1. Flowchart of the literature search and study inclusion.

ranging from 0 to 0.57. At the same time, all the six studies showed a lower infection sign (Table 2). Neut et al. [31], demonstrated PLGA (Poly-lactic-co-glycolic acid)-gentamicin-HA (hydroxyapatite)-coated pins showed lower fixation strength than HA-coated pins at 4 weeks, but the mechanical strength of the interface after 12 weeks was higher for the PLGA-gentamicin-HA-coated pins.

Among the six studies that assessed silver surface modification, three rat models and three rabbit models were used. Of these, three studies reported a lower infection rate with RR ranging from 0.13 to 0.71. Moreover, five studies found a lower bacterial load or infection sign (Table 2). While the elevated mean silver concentrations in the blood or organs were reported in two studies [19,34], no side effects were reported.

Another two studies employed copper and Cationic Steroidal Antimicrobial-13 (CSA13) modifications in rabbit and sheep animal models, respectively. With the copper modification, the RR was 0.25 without liver or kidney side effects detectable during the experimental period. Cationic Steroidal Antimicrobial-13, which is a cholic acid derivative, showed lower infection risk (RR = 0.52) with good biocompatibility. The basic experiment details are reported in Table 2.

3.4. Clinical study

There were five studies using silver coating of the prosthesis to prevent infection in patients with high infection risk, such as immunosuppressed patients or patients with tumor (Table 3). Among them, three retrospective studies compared the infection rate between patients using silver modified implants and patients without silver modified implants and another retrospective cohort study assessed reinfection rate after cured PJI. The RR for (re)infection ranged from 0.24 to 0.70. Schmolder et al. [43] reported ten of 100 patients (10%) underwent revision for PJI after using the silver-coated mega prostheses in a case series.

There were two case series using iodine-modified implants to prevent PJI. Shirai et al. reported the incidence of infection was 5% (1/21) [44] while Kabata et al. reported all of the 21 patients with immunosuppressed status or tumor with iodine coating did not reveal evidence of an infection [45]. Details of the included case series are presented in Table 3.

4. Discussion

Although conventional strategies, such as laminar flow and antibiotics, have predominated in the current prophylaxis of infection in orthopedic procedures [46], the incidence of PJI after joint replacement persists in 1%–2% of cases. Due to the significant burden that patients can experience from PJI [7,47], preventing PJI would benefit both patients and surgeons. Considering promising antimicrobial performance of modified surfaces [18,48], it has been proposed that implants with antimicrobial properties may provide a new avenue of prevention to address PJI [49,50]. However, in vivo studies have the potential to provide more clinically relevant details than in vitro studies due to conditions that are more analogous to human bodies. To the best of our knowledge, this is the first systematic review focused on the preclinical and clinical evidence about prophylactic effects against PJI with prosthetic surface modifications.

Table 2
Details of the included animal studies.

Animal study										
Studies using antibiotic modification										
Author/year	Animal	Site	Implants	Pathogen	Surface modification	Sample size	Infection rate	RR	Infection sign	Side effect
Alt et al. [28] (2006)	Rabbit	Tibia	Kirschner wire	S.a	GEN-RGD-HA-steel	10	0/10 (0%)	0	Lower histological sign	—
					GEN-HA-Steel	10	0/10 (0%)			
					HA-Steel	8	7/8 (88%)			
Antoci et al. [29] (2007)	Rat	Femur	Rod	S.a	VAN- Ti	12	—		Fewer bacterial culture	—
					Ti	12			Lower radiological infection sign	
Bernthal et al. [30] (2010)	Mouse	Femur	Kirschner wire	S.a	RIF-MIN-steel	—	—		Lower infective bioluminescent signals	—
					Steel					
Neut et al. [31] (2015)	Rabbit	Femur	Pin	S.a	PLGA-GEN-HA-Ti	7	0/7 (0%)	0	Lower histological sign	Lower fixation at 4 weeks, but higher fixation at 12 weeks.
					HA- Ti	7	7/7(100%)			
Min et al. [32] (2016)	Rabbit	Tibia	Pin	S.a	GEN-BMP-PEEK	12	—		Fewer bacteria amount	—
					GEN-PEEK	12			lower infective sign in bioluminescence and SEM	
					BMP- PEEK	12				
					PEEK	12				
Stavrakis et al. [33] (2016)	Mouse	Femur	Kirschner wire	S.a	PEG-PPS-TIG-Ti	7	0/7 (0%)	0; 0.57	Lower radiological and bioluminescent sign;	—
					PEG-PPS-VAN-Ti	7	4/7(57%)			
					PEG-PPS Ti	7	7/7(100%)			
Studies using silver modification										
Gosheger et al. [34] (2004)	Rabbit	Femur	Endoprost-hesis	S.a	Ag- Ti	14	1/14 (7%)	0.15	Lower histological sign	Elevated silver level without pathologic changes
					Ti	15	7/15 (47%)			
Akiyama et al. [19] (2013)	Rat	Tibia	Rod	MRSA	Ag-HA-Ti	20	—	—	Fewer bacteria culture lower radiographic/ histological sign	Elevated silver level
					HA- Ti	20				
Bitika et al. [35] (2013)	Rabbit	Knee	Endoprost-hesis	S.a/P. a	Ag- Ti	24	17/24 (71%)	0.71	—	—
					Ti	24	24/24 (100%)			
Kose et al. [36] (2013)	Rabbit	Femur	Pin	MRSA	Ag-Ti	9	1/9 (11%)	0.13	Lower radiographic/ histological sign	—
					Ti	9	8/9 (89%)			
Cheng et al. [37] (2013)	Rat	Tibia	Rod	MRSA	Ag–Ti	10	—	—	Lower radio-graphic/histological sign	—
					Ti	10				
Qin et al. [20] (2014)	Rat	Tibia	Kirschner wire	S.e	Ag-nano-Ti	30	—	—	Fewer bacteria culture lower radiographic and histological sign	—
Studies using other modifications										
Sinclair et al. [38] (2013)	Sheep	Femur	Plug	MRSA	CSA13-Ti	5	1/5 (20%)	0.25	Lower histological sign	No difference in biocompati-bility/bone ingrowth
					Ti	3	3/3 (100%)			
Mauerer et al. [39] (2017)	Rabbit	Femur	Bolt	S.a	Cu-TiO2	12	5/12 (42%)	0.52	Lower haematological infective sign	

RR: risk ratio; Ag: silver; Ti: Titanium; HA: hydroxyapatite; GEN: gentamicin; RGD: arginine-glycine-aspartic acid peptide; VAN: Vancomycin; RIF: Rifampin; MIN: Minocycline; PLGA: poly (lactic-co-glycolic acid); BMP: bone morphogenetic protein; PEG-PPS: poly(ethylene glycol)-poly(propylene sulfide); TIG: Tigecycline; CSA13: cationic steroidal antimicrobial-13; Cu: copper; S.a: Staphylococcus aureus; MRSA: Methicillin-resistant Staphylococcus aureus; P. a: Pseudomonas aeruginosa; S.e: Staphylococcus epidermidis; SEM: scanning electron microscope: —; Not mentioned.

Table 3
Details of the included clinical studies.

Clinical study										
Studies using silver coated implants										
Author/year	Study design	Indication	Implant	Surface modification	Sample size	Gender M/F	Age (year)	(re)Infection rate	RR	Possible Side effect
Hardes et al. [21] (2010)	Retrospective Cohort	Tumor	Mega-prostheses	Ag-Coated	51	20/31	37(10–78)	3/51 (5.9%)	0.33	One case with suspected local argyrosis
				Uncoated	74	—	—	13/74(17.6%)		
Hussmann et al. [40] (2013)	Retrospective Cohort	Tumor/Cured infection	Mega-prostheses	Ag-Coated	18	6/12	60.1 ± 19.4	1/18 (5.6%)	0.24	No side effects
				Uncoated	31	13/18	72.9 ± 14.3	7/31 (22%)		
Wafa et al. [41] (2015)	Retrospective Cohort	Tumor/ Cured infection/ Chemo-therapy	Mega-prostheses	Ag-Coated	26	—	—	8/46 (17.4%)	0.53	—
				Uncoated	24			14/43 (32.6%)		
Zajonz et al. [42] (2017)	Retrospective Cohort	Cured infection	Mega-prostheses	Ag-Coated	20	9/11	74(46-83)	8/20 (40%)	0.70	—
				Uncoated	14	6/8	69(35-87)	8/14 (57%)		
Schmolders et al. [43] (2017)	Case Series	Tumor	Mega-prostheses	Ag-Coated	100	52/48	55 (12–82)	10/100 (10%)	—	—
Studies using iodine supported implants										
Shirai et al. [44] (2014)	Case series	Tumor	Mega-prostheses	Iodine-Supported	21	—	—	1/21 (5%)		Two cases with mechanical implant failure. No thyroid gland malfunction
Kabata et al. [45] (2015)	Case series	Immmuno-suppressed/ Cured infection	Hip prostheses	Iodine-Supported	21	—	—	0/21 (0%)		No case of thyroid gland malfunction

RR: Risk ratio; Ag: silver; M/F: male/female; —: Not mentioned.

Surface modification with antibiotics is a promising method for imparting infection prophylaxis. Topical application of antibiotics has been proven effective to prevent deep infection in spinal surgeries [51], but its efficacy in joint arthroplasty has not been determined [52]. As high antibiotic concentration in the early period and prolonged release is critical for preventing PJI [53,54], kinetics may be the reason for the undetermined efficacy of antibiotic powder in joint arthroplasty because antibiotic powder would dissolve and be metabolized quickly. Antibiotics from the modified surface could release into surrounding tissues and achieve concentrations above the minimum inhibitory concentration (MIC) for a longer time than antibiotic powder [31,33]. When antibiotic modified implants are used clinically, there are two factors that cannot be ignored. The first one is pathogen diversity that is associated with PJI. While *Staphylococcus aureus* and *Staphylococcus epidermidis* are the two dominant pathogens for PJI after joint replacement, other bacteria remain responsible for nearly one-third of PJI cases [55,56]. Implants with specific antibiotics can only prevent specific susceptible pathogens. Another factor to consider is antibiotic resistance. Gentamicin, which is commonly used in these animal studies, is reportedly resistant in up to 40% of *S. epidermidis* and 32% of *S. aureus* cases [57,58]. The resistance of methicillin is on the rise and the susceptibility of vancomycin is also decreasing in the methicillin-resistant *S. aureus* (MRSA) subgroup [2,59]. One of the possible benefits of surface modification is that the comparatively high antibiotic concentration may still prove effective for bacteria that may other prove resistant as a result of low antibiotic blood concentration, but more evidence is needed to determine this. Moreover, an additional two phenomenon may also impair prophylaxis against infection with these antibiotic surfaces. The first one is the eagle effect, in which bacteria or fungi exposed to concentrations of antibiotics higher than the optimal bactericidal concentration have paradoxically improved levels of survival and may bring risk for persistence of bacteria [60]. Given that the release of an antibiotic via these surface modifications may yield a high tissue concentration, the eagle effect is possible. Another phenomenon is that when the released concentration ends up being lower than the MIC, it may predispose to long-term relapse [61].

Silver modified implants also showed lower infection risk in both animal models and clinical studies. The anti-biofilm mechanism of silver has been studied previously. A change in permeability of the cell membrane, inactivation of enzymes and peptides and formation of free radicals are the possible mechanisms [62,63]. Several factors may lead to the underestimation the infection prophylactic effects of silver modified implants in clinical studies. The first one is the choice of indication. We noticed that most indications in the included publications are musculoskeletal tumors or immunosuppression status, which is of high risk for PJI. It confers an unequal risk to develop PJI for each patient [64] and may substantiate the high cost of these modified implants. The second one is the combined usage of antibiotics in clinical cases, which may reduce infection rate in both the control and experimental groups at the same time, making the infection prophylactic effect(s) of silver modified implants alone difficult to evaluate. However, despite these possible reasons for

underestimation of silver modification, these implants still showed lower infection risk for these patients. Similar to antibiotics, resistance may also impair the prophylaxis against PJI with metal surface modifications. Clarifying the mechanism, such as genetic mutation and plasmids horizontally transference, may help to cope with possible resistance of these metal surface modifications [65,66].

While surface modifications have promising antimicrobial effects, side effects remain a major concern. Toxicity is the first concern pertaining to these modifications. With a silver coating, the elevated silver concentration in the blood or in organs has been proven by Gosheger et al. [34], while there were no detectable clinical side effects in this study. The silver ion concentration was lower than the reported harmful concentration, which could be an explanation. Argyria, a disease caused by physiologic silver ion overload, was reported in nearly 22% patients who have received silver-coated prostheses [67]. Therefore, the release of silver ions to the human body after implantation of silver–coated prostheses should be investigated [52]. Impaired osteointegration, which is a special concern for arthroplasty, were generally tested in in vitro co-culture models [68]. But in vivo information is more clinically related. Neut et al. [31] did not find impaired osteointegration. The PLGA-gentamicin-HA-coated pins demonstrated lower fixation strength than HA-coated pins at four weeks, but higher mechanical strength at twelve weeks. The results were different from previous in vitro studies, which reported that the high concentration of antibiotics would impair the osteoblasts [69,70].

There are several limitations in our review. First, although we identified 21 studies that were eligible for inclusion in this review, the study designs and methods were heterogenous, which makes the meta-analysis inapplicable. Different animal models were used, but most of them were rat or rabbit except one sheep model, which are the commonly used animal models. Lower infection risk showed in all the different animal models and clinical studies after using the included modified surfaces. Thus, it could provide positive value about the prophylactic effect against PJI without meta-analysis. Since animals such as mice are too small to use prosthetic joint. This may bring some bias for the conclusion about osteointegration to generalize in clinical cases but no bias for prophylaxis effect against PJI. Second, sample size in these clinical studies were small and no prospective randomized clinical trials were carried out, which is difficult to carry out to investigate the prophylactic effect of modified prosthesis. But all these included comparative clinical studies showed lower PJI risk, which could help to determine the positive infection prophylactic effect. Data from registration should be pursued for more clinical evidence. Third, most patients used megaprostheses in these studies, which may be a little different from primary joint prostheses. However, the mechanism of PJI and the prevention methods are the same in these joint implants and the information is still helpful in terms of prophylactic effect(s) against PJI in joint arthroplasty. At last, there are some new prosthesis coating techniques, like UV-activated coating, polymer surfaces, carbon coating, and so on [71,72], which have not progressed to in vivo experiments. This review will need to be updated in due course in order to maintain currency with the rapidly-evolving techniques and thriving science.

5. Conclusion

Surface modification, especially antibiotic and silver modifications, are helpful to prevent PJI in both preclinical animal and clinical trials.

Disclosure of interest

The authors declare that they have no competing interest.

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Authors' contribution

Wang Deng: Conception and design of the study. Collecting, analyzing and interpreting the data. Drafting, revising and approving the manuscript.

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Appendix A. Supplementary data

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