the revision rates due to infection in primary uncemented THA with those of cemented THA with antibiotic-loaded cement and to those of cemented THA without antibiotic-loaded cement. The results showed that the risk of revision due to infection was the same for uncemented and cemented arthroplasties with antibiotic-loaded cement, but higher for cemented arthroplasties without antibiotic-loaded. The authors proposed that cementation might cause bone necrosis, either by direct toxicity or by the generation of heat during the polymerization process. The necrotic bone was susceptible to the growth of bacteria, which appeared to be neutralized by adding antibiotic to the cement.

Cemented vs. Uncemented TKA

Although there are several published RCTs and systematic reviews comparing the survival of cemented versus uncemented TKA, few present PJI as the primary endpoint. A Cochrane review from 2012 comparing fixation methods in TKA was unable to report on superficial or deep infection rates due to inconsistent reporting of data in the included studies [21]. Similarly, the various retrospective studies and RCTs have not demonstrated a significant difference in the incidence of PJI between the fixation methods [22-26]. However, like the studies on THA fixation, they have low enrollments and are not appropriately powered to assess for a difference in PJI.

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QUESTION 3: Does the surface (grit-blasted, plasma-sprayed, porous metal, porous beaded and hydroxyapatite (HA) coated) of uncemented total hip arthroplasty (THA) components influence the rate of subsequent surgical site infections/periprosthetic joint infections (SSIs/PJIs)?

RECOMMENDATION: The surface roughness, including porosity size, geometry and symmetry determines biocompatibility. Several studies have shown that the surface material influences bacterial adherence, with an ideal pore size dependent on bacterial size. Too small a pore size does not allow bacterial lodging. In recent studies, nanotexture of material has been found to be important with some surfaces with nanotubules showing anti-infective properties.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 61%, Disagree: 20%, Abstain: 19% (Super Majority, Weak Consensus)

RATIONALE

Multiple antimicrobial coatings have been proposed in total joint arthroplasty, including silver nanoparticles, sol-gel, and hydrogel synthetics, as well as direct covalent modifications of metallic and polyethylene materials. In fact, the European Commission has recently funded a four-year initiative to establish a network of institutions involved in the development of new antimicrobial coatings to prevent healthcare-associated infections [1]. Most of those efforts so far have been limited with few implants involving antibiotic doping of hydroxyapatite (HA) layers of polyethylene with long term concerns for implant survival and antibiotic resistance development.

Nevertheless, titanium (Ti) itself comes in different forms, alloys and surfaces that may present different propensities for bacterial colonization in the face of osteointegration. Most Ti implants undergo passivation before surface modification. Passivation involves the treatment of Ti by acid, electropolishing, anodizing and oxidation. The process results in surface cleaning and removal of iron and other exogenous materials, as well as a production of a surface Ti oxide layer. The side effect of passivation is often a change in surface topography and charge. Piranha etch (H_2SO_4/H_2O_2) has been previously described for passivation but significantly changes the surface topography. Prior studies have shown that hydrothermal aging was a better way of passivating orthopaedic Ti alloys as it preserved the desired surface topography [2]. The resultant Ti oxide layer is highly biocompatible and can enhance cell adhesion and proliferation [3,4]. Increased host cell biocompatibility may result in decreased infection. Gristina et al. [5] has postulated the race for the surface describing periprosthetic infection and host cell integration/biocompatibility as competing processes and suggesting as far back as 1987 that "modifications to biomaterial surfaces at an atomic level will allow the programming of cell-to-substratum events, thereby diminishing infection."

No clear quantitative research has delineated the role of nanoscale morphology on infection [6]. Several studies have examined the interaction between the surface and various proteins. This adherent extracellular matrix directly drives and signals cell interactions at the biomaterial surface. The outer membrane of a typical cell contains many receptors that look and interact with its environment at the macro- and micromolecular levels. More than 20 members of the integrin receptor family have been identified and their interaction with motifs such as Arg-Gly-Asp (RGD) within fibronectin and vitronectin have been described [7]. These receptors interact with the surface topography including grooves and ridges [8]. Nanoscale modulation of implant surface topography can drive cell adhesion, motility, activation of tyrosine kinases and gene expression. Even though it was originally thought to be the dimensions of the topographical features that determine cell interactions, the shape and symmetry of surface features are just as crucial [4]. Zinger et al. [9] has shown an impressive variety of responses dependent on the microarchitecture of the Ti surface. Osteoblasts favored larger cavities for attachment and growth, with sub-micron-scale etching enhancing differentiation. In contrast, prostaglandin synthesis was dependent on the cavity dimensions but not the sub-micron scale. Prostaglandins are important in cellular response to infection, and thus surface topography may modulate periprosthetic infection.

Interestingly, bacteria have also been shown to interact with the surface, frequently exhibiting similar propensities for biomaterials as osteoblasts. Truong et al. [10] have shown that *S. aureus* had a preference for granular Ti surfaces while *Pseudomonas* preferred polished surfaces. Singh et al. [6] show that the increase in surface pore aspect ratio and volume, related to the increase of surface roughness, improves protein adsorption, which in turn downplays bacterial adhesion and biofilm formation. As roughness increases up to about 20 nm, bacterial adhesion and biofilm formation are enhanced; further increase of roughness causes a significant decrease of bacterial adhesion and inhibits biofilm formation. Lorenzetti et al. [11] suggest that the pore size correlates to the size of the bacteria, where in, too small a size does not allow bacterial lodging into the space while too large a size does not allow the bacteria to hide from the surrounding environment and the host. Studies have shown that over 90% of *S. aureus* express either fibronectin binding proteins, fibrinogen binding proteins or collagen binding proteins, with almost 60% of bacteria expressing all of these proteins [12]. More worrisome, these genes were significantly more common in methicillin-resistant *S. aureus* (MRSA) than in susceptible strains. These cell surface receptors give bacteria an advantage for surface and extracellular matrix interactions that ultimately may allow them to outcompete osteoblasts for surface propagation.

The differential response of osteoblasts and bacteria to titanium topography raises the question regarding the specific interactions on commercially available titanium surfaces. Modern implants have gone through several iterations of surface topography changes, most recently with three-dimensional printing. Surface roughening of titanium produces topography that is biocompatible and improves osteoblast adhesion, proliferation and differentiation [13]. Much less is known about the bacterial response to these surfaces.

Grit blasting involves pressurized particle projection using ceramic or silica materials onto the implant surface. The process always involves a subsequent acid etching to remove any contaminants that could have been deposited on the surface. Al-Radha et al. [14] have examined the effect of zirconia, Ti blasted with zirconia, Ti blasted with zirconia followed by acid-etching, as well as polished Ti surfaces on bacterial colonization. The Ti blasted with zirconia reportedly showed lower bacterial adhesion, but that was in the presence of saliva. The base surfaces showed no difference in terms of bacterial colonization, even between polished and blasted surfaces. The average surface roughness in this study was about 0.16 um for the zirconia blasted surfaces.

Plasma spray coating involves thick layer deposition of materials such as Ti or HA, usually by spraying the melted material onto the substrate. Plasma spray is theoretically better controlled than grit blasting and exhibits the highest surface roughness compared to acid etching or grit blasting. Knabe et al. [15] report an average roughness of 3.43 um for plasma sprayed Ti and 2.07 for HA coated Ti. Interestingly, they also show that HA sprayed surfaces had significantly less bone contact.

HA coating is used for total hip coatings due to its presence in normal bone and the potential biocompatibility and osteoconductivity. Synthetic calcium phosphate ceramics have similar chemical and crystalline properties to biological apatite crystals. HA is the most similar to biological crystals while being the least soluble of all calcium phosphate ceramics [16]. Interestingly, in an analysis of 116,069 THAs using the Nordic Arthroplasty Register Association database, Hailer et al, [17] found no difference in revision rate between HA coated and uncemented porous or rough sand-blasted stems. Despite extensive mentioning of anti-infective properties of HA coating in the literature, the potential benefit would only be secondary to possible earlier osteoblast deposition on the surface, with no clear antibacterial effects studied or reported.

Ultimately, most studies of surface topography, surface roughening and implant surface design focus primarily on osteocompatibility. Even though surface roughness influences bacterial adhesion and survival, we were not able to identify any well controlled studies on bacterial growth on different orthopaedic implant topographies. Large registry studies show largely no difference of survival between various implants. Perhaps the material itself, such as tantalum [18], may provide an advantage in the face of periprosthetic infection. Nevertheless, roughened Ti surfaces definitely provide an osteoconductive advantage. Considering the "race for the surface" theory, such materials should then provide a certain competitive advantage against infection, even though we have a hard time recommending a specific surface topography at this time. Further research, new techniques in surface preparation, and the advantage of designer surfaces will likely allow for further delineation of this question in the near future.

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QUESTION 4: Does the type of bearing surface influence the incidence of surgical site infections/periprosthetic joint infections (SSIs/PJIs) after total hip arthroplasty (THA)?

RECOMMENDATION: There is a higher incidence of PJIs with metal-on-metal (MoM) THA; however, there is no difference in risk of PJIs among other bearing surfaces.

LEVEL OF EVIDENCE: Strong

DELEGATE VOTE: Agree: 84%, Disagree: 10%, Abstain: 6% (Super Majority, Strong Consensus)

RATIONALE

THA bearing surfaces have been developed primarily to optimize wear properties. However, there has been recent interest in differing propensities for infections among bearing types. It has been hypothesized that some bearing couples may have a disproportionately negative influence on local tissue immunocompetence, resulting in development of clinically manifested PJI that would otherwise remain silent [1].

In a study of 276,878 patients from the Australian Orthopaedic Association National Joint Replacement Registry, a higher rate of revision for PJI was observed with large-head MoM THA as compared to other bearing surfaces [2]. In a smaller retrospective case series of 124 patients, MoM THA had a 4-fold higher infection rate than historical cohorts of other bearing surfaces from the same institution [3]. Furthermore, Lee et al. performed a meta-analysis comparing MoM to ceramic-on-ceramic bearings, finding MoM bearings were associated with a higher risk of revision for PJI (odds ratio (OR) = 6.21, p = 0.015) [4].

Multiple prospective randomized trials, as well as a systematic review/meta-analysis, have demonstrated no difference in infection rate between metal-on-polyethylene, ceramic-on-ceramic, and ceramic-on-polyethylene bearings [5–8]. Hu et al. performed a meta-analysis of five randomized controlled trials comparing ceramic-on-ceramic and metal-on-polyethylene bearings and found no difference in deep infection rate [9]. A registry study by Pitto et al. found ceramic-on-ceramic bearings to have a lower risk of revision for PJI compared to other bearings [10]. However, this work did not incorporate Body Mass Index or medical comorbidities into its multivariate analysis, which are known to have a significant effect on PJI risk [11].