Nanoparticles in Joint Arthroplasties

Rebecca J. Thomson, Afton K. Limberg, Douglas W. Van Citters
Thayer School of Engineering, Dartmouth College
15 Thayer Drive, Hanover, NH 03755, U.S.

Joint arthroplasty, specifically total knee arthroplasty (TKA) and total hip arthroplasty (THA), are two of the highest value surgical procedures. Over the last several decades, the materials utilized in these surgeries have improved and increased device longevity. However, with an increased incidence of TKA and THA surgeries in younger patients it is crucial to make these materials more durable. The addition of nanoparticles is one technology that is being explored for this purpose. This review focuses on the addition of nanoparticles to the various parts of arthroplasty surgery comprising of the metallic, ceramic or polyethylene components along with the bone cement used for fixation. Carbon additives proved to be the most widely studied, and could potentially reduce stress shielding, improve wear and enhance the biocompatibility of arthroplasty implants.

Keywords: Total knee arthroplasty, total hip arthroplasty, polyethylene, carbon

1. Introduction

Total joint arthroplasty is often described as one of the most successful elective surgical procedures when device longevity and patient satisfaction are concerned. The positive outcomes that come with a relatively low cost result in a high value operation for millions of patients annually. With an aging population these procedures, specifically total knee arthroplasty (TKA) and total hip arthroplasty (THA) have become increasingly frequent. However, these surgeries are not faultless and can end in failure. The most common modes of failure include loosening of the implant; periprosthetic joint infection; wear; and pain[1-3].

Traditionally total joint arthroplasty implants consist of a bearing couple of metal on polyethylene, metal on ceramic, metal on metal or ceramic on ceramic[4-6]. Choosing the couple and the precise implant materials is an important consideration for surgeons when performing both TKA and THA. Each combination has advantages and disadvantages and can be chosen depending upon patient activity level, patient demographics and material properties. The drawbacks associated with each of these materials has driven scientists and engineers to investigate the use of nanoparticles to improve their mechanical, tribological, and biological properties.

Nanoparticles, defined herein as materials with at least one dimension on the scale of 1-100 nm, are an evolving technology that are being incorporated into arthroplasty materials to improve on deficiencies leading to failure. The use of nanoparticles spans a wide range in arthroplasty, from improving antibiotic release in bone cement, to implant coatings for enhanced osteointegration, to carbon fiber composite implants to reduce stress shielding. The advancements in nanotechnology continue to push the boundaries in arthroplasty to improve patient outcomes. The present review shall focus on the use of nanoparticles in TKA and THA materials given the relative magnitude of these surgeries relative to other arthroplasty procedures. The objective is to orient the reader to the last decade of research directly related to these materials in arthroplasty, and identify key areas needed for progress in this field.

2. Methods

Two different databases, Pubmed and Web of Science, were searched for articles relating to nanoparticles in joint arthroplasty. To ensure contemporary science was covered, only articles published from 1/1/2010 to 9/1/2022 were included in this review. All articles had to be available in English, and the full text had to be available. Articles studying wear particles coming from the implants were excluded.

The search terms relating to 'nano-' were: nanoparticle, nanofiber, nanocomposite, nanostructure, nanocoating, carbon fiber, carbon-fiber, or metal nanoparticle. These terms were combined with arthroplasty specific search terms which included: bone cement, joint replacement, arthroplasty, unicondylar revision, implant, or joint arthroplasty. Finally, the search was limited by specifying the joint which for our search included shoulder, hip, knee, and ankle.

A total of 92 articles were reviewed. This included 12 review articles or book chapters relating to nanoparticles in the joint arthroplasty materials.

Additionally, it should be noted that carbon fiber, while not always on the nano scale, was included for this review as this material has played a key role in the story of nanoparticles in joint arthroplasty materials. Moreover, the use of carbon fiber with diminishing diameter continues to be investigated in the realm of orthopedics as it has promising mechanical and tribological properties.

3. Results

Literature review revealed nanoparticles are incorporated into four classes of materials including coatings and lubricants, polymers, ceramics, and metals. Where found, biocompatibility results are highlighted though the reader will find that work remains to be done in this area.

3.1. *Coatings and Lubricants*

Nanomaterials in coatings and lubricants for arthroplasty are dominated by reports on applications of carbon allotropes, titanium, and to a lesser extent degradable polymers.

Carbon is known to have many advantageous mechanical properties in the body as well as antibacterial characteristics. Additionally, diamond-like carbon coatings are being investigated for their use in orthopedics. These diamond-like coatings are proposed to reduce the wear of implants, hopefully leading to less loosening failures. The tribological properties of carbon coatings applied to both metal implants as well as polyethylene implants have been described[7,8]. These studies showed that the carbon coatings had no cytotoxic effects, and the addition of the coatings improved wear resistance compared to the traditional cobalt chromium or titanium alloy and ultra-high molecular weight polyethylene (UHMWPE) interface. Total hip wear simulator tests have also shown decreased wear with nanocrystalline diamond coatings[9]. These authors also mention that the carbon coating could decrease the inflammation effects seen when wear particles are generated due to the bio-inertness of carbon. Furthermore, one study demonstrated the ability of nano-diamond particles to reduce the number of Staphylococcus aureus cultures *in vitro*, while also reducing friction at the metal-poly implant interface[10]. Another study looking at the cytotoxicity of graphite nanoparticles that are generated by these diamond-like carbon coatings did notice significant dose dependent effects *in vitro* when the wear particle biological load was over 30 μg/mL[11]. It will be important to keep this dose dependent effect in mind as these coatings are further studied.

Kang et al.[12] utilized finite element analysis (FEA) to evaluate weight loss under depth and kinematics under gait-loading conditions for four different surface properties including: nanostructured diamond, diamond-like carbon, titanium-nitride, and oxidized zirconium. From this analysis, the authors determined that oxidized zirconium had the lowest wear rate, weight loss and wear depth of all the surface properties.

Other coatings that have been studied in the literature include hexavalent chromium electrolyte, and C_{60} with the addition of fullerene nanoparticles both of which showed improved wear resistance but had limited literature sources[13]. Silver is another element that has been utilized as a coating material[14,15]. Silver has good antibacterial effects, however there is disagreement whether it can be toxic *in vivo*. Different methods for cytotoxicity studies have shown dissimilar results, and the toxicity may be related to the nanoparticle size[16,17].

The addition of nanotubes to metallic implant surfaces is similarly being explored for improved bone interaction and infection treatment. First, nanotubes can promote osteointegration by providing an ingrowth surface for osteoblasts[18,19]. Both carbon and titanium nanotubes are being studied in this regard and several different implant materials have been analyzed including, ceramic, cobalt-chromium and titanium. One study noted marginally better osteointegration with the titanium nanotubes over other canidates[20]. The authors hypothesized this could be due to the better organization of the titanium nanotubes compared to the carbon nanotubes. Titanium nanorods have also shown to promote osteointegration *in vitro*[21].

With infection being one of the most complex and difficult to treat failure mechanisms in joint arthroplasty, the use of nanotubes for sensing, prevention, or treatment could provide new ways to approach this problematic complication. It is thought that severity of infection might be reduced if bacterial biofilms can be prevented. Carbon nanotubes have been shown to reduce the presence of these biofilms, specifically against MSRA biofilms[22]. After an infection sets in, the use of nanotubes has also been explored when integrated into a nanocomposite film that could monitor the pH of the joint via tomographic imaging to watch for pH changes that could relate to infection[23]. Finally, titanium nanotubes have been shown to assist with antibiotic release to treat periprosthetic joint infections (Fig. 1)[24].

Polymeric nanofiber coatings to treat infection are also being explored. Using a mouse model, one study looked at the effects of a PLGA coating that would provide local antibiotic delivery as well as prevent biofilm formation[25]. Electrospinning of PLGA and PCL to create a lattice coating over the implant surface proved to have a significant antibiotic release over 6 weeks[26].

3.2. *Structural Polymers*

Polymers are a class of materials used in multiple aspects of arthroplasty procedures such as adhesion, bearings, and other structural components of the implants. Addition of nanoparticles to polymers has been a continued effort to increase the strength, biocompatibility, and potential for application in human patients.

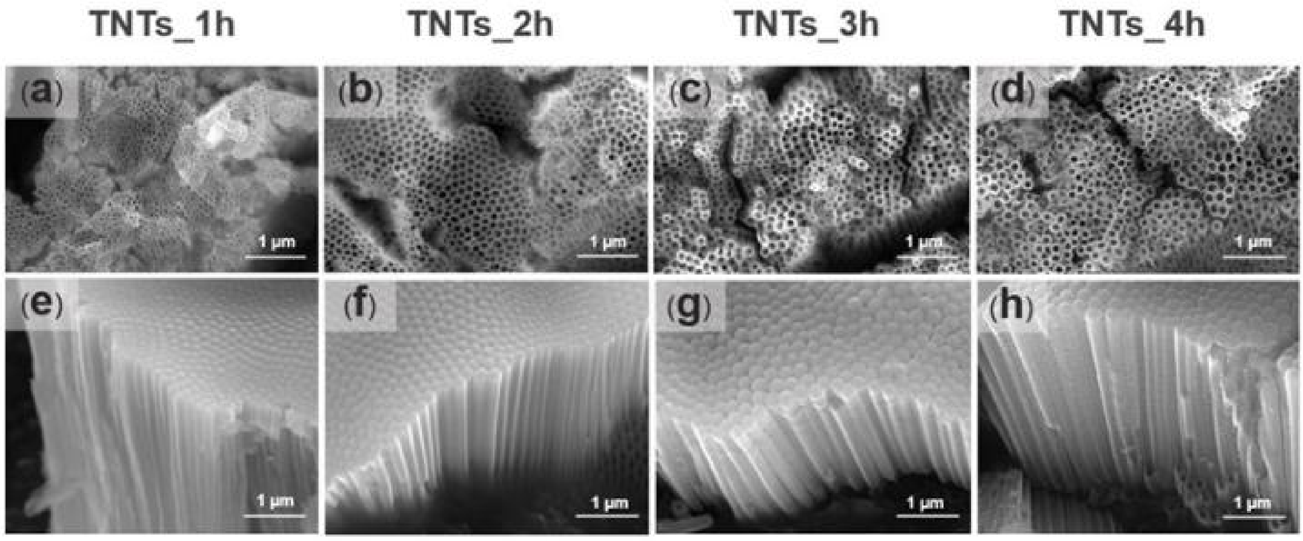

Fig 1. FESEM micrographs of tope and side views of titanium oxide nanotubes at 1h, 2h, 3h, and 4h from left to right. Pore diameters of nanotubes increased and length decreased when time of anodization increased. Adapted from *Materials*[23].

3.2.1 *Bone Cement*

Poly-methyl methacrylate (PMMA) bone cement has been employed as a fixation material in joint arthroplasty since the very first total hip replacements. In addition to its ability to provide a stable union between the implant and surrounding bone, PMMA is employed as a delivery medium for antibiotics. This becomes particularly important during revision procedures for infected joints. Exploiting nanotechnology in bone cement has been studied in the context of its structural benefits and its drug-eluting character.

Wang et al. report adding multi-walled carbon nanotubes to PMMA to increase osteointegration at the bone-cement interface. Both *in vitro* and *in vivo* animal studies have shown promising results[27] wherein the weight percent of multi-walled carbon nanotubes correlated with biocompatibility and osteointegration. Positive outcomes are attributed to increased osteogenic differentiation of cells when exposed to the nanotubes as assessed at both the gene and protein levels. A notable benefit of this addition is that the PMMA composite density is decreased while mechanical properties such as hardness and elastic modulus increased[28].

Antimicrobial nanoparticles such as gold and silver have also been considered as additives to bone cement. The main concern with this alternative to pharmaceuticals is whether the metals will affect the mechanical properties of the bone cement. One hypothesis is that the nanoparticles create weak points due to discontinuities in the cement structure. However, a lower weight percent of gold nanoparticles, on the order of 0.25 wt%, did not significantly alter the compressive strength while exhibiting good antibacterial properties[29]. It should be noted that recent literature suggests that the antibacterial nature of silver is due more to the diffusive dynamics of the silver ions than the size of the particle itself. Instead, nanoparticles provide a very high surface area to volume ratio, maximizing the antibacterial activity[30].

3.2.2 *Carbon Fiber Reinforced Polyether-ether-ketone (CFR-PEEK)*

Carbon-fiber reinforced polyether-ether-ketone (CFR-PEEK) has been investigated as an alternative to conventional UHMWPE and other bearing materials for many years. CFR-PEEK has many potentially beneficial characteristics such as reduction in wear particle volume, reduction in stress shielding, better bone-material mechanical property compatibility, and no risk of metal ion release. Many studies have investigated the biotribology, mechanical properties, wear particle biocompatibility, stress and strain distribution, and other properties of CFR-PEEK. Most contemporary articles revealed in the literature review focus on the wear properties and wear particle biocompatibility of CFR-PEEK compared to UHMWPE. Studies ranged from computational, to benchtop, to *in vivo* models.

In vivo testing for joint arthroplasties is expensive, time consuming, and inefficient. With increasing computational power, FEA models have increased in prevalence and accuracy for screening of new biomaterials in orthopedic applications. While computational wear prediction requires additional development, many validated models analyze von Mises and contact stresses. Despite fidelity of the models to experimental results, it should be warned that a limit of many of these models is the assumptions made about physiological parameters as well as on isotropy of materials and tissues.

CFR-PEEK has previously been reported to have higher wear resistance, hardness and yield strength compared to standard UHMWPE, and this change can be attributed in part to the promotion of the thermoplastic matrix integration with the incorporated fibers[31]. Kwak et al. modeled the biomechanical effects of CFR-PEEK, PEEK and UHMWPE on unicompartmental knee arthroplasties using von Mises stress evaluation to determine aseptic loosening and anteromedial pain in the tibia[32]. They concluded

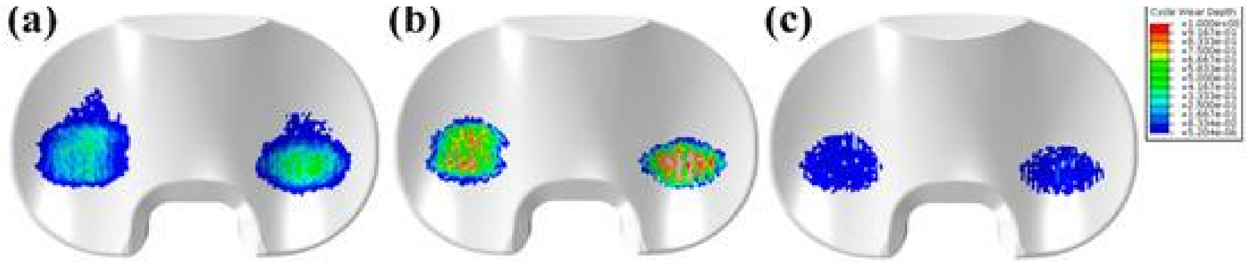

Fig 2. FEA predicted wear depth for a) UHMWPE, b) PEEK, and c) CFR-PEEK, adapted from *Lubricants*[36].

that CFR-PEEK could be used as an alternative to UHMWPE for tibial inserts due to it showing the lowest contact stress on lateral meniscus and tibial cartilage. Another study investigated the biomechanical effects of varus/valgus alignments of UHMWPE and CFR-PEEK from 9 degrees of varus to 9 degrees of valgus in UKAs[33]. For CFR-PEEK, the valgus condition should be avoided and varus conditions from 1 up to 6 degrees showed similar biomechanical output and is recommended for UKA. A TKR FEA concluded that CFR-PEEK and PEEK could be used as alternate bearing materials but should be cautious if planning to use either for a cruciate retaining TKA[34].

In an alternative application for tumor-type distal-femoral prostheses CFR-PEEK has the same stability as the CoCrMo but lower density, good light transmittance and good mechanical fit which makes it a good alternative material for distal femur and extension rod for the distal femoral prosthesis[35]. Only limited FEA wear testing has been performed, with wear models built on mechanical properties of the material. These models have concluded that CFR-PEEK could be a good alternative, when looking at kinematics, wear depth and volumetric wear, to UHMWPE for tibial inserts [33,36](Fig 2). Such simulations failed to incorporate micro-scale and nano-scale interactions between the fibers and the matrix, and the fibers and the counterface.

Owing to the complex motions and contact conditions associated with human joints, preclinical wear testing for eventual arthroplasty applications is more typically performed using pin-on-disk, ball-on-disk, and joint simulators. Grupp et al. looked at the in vitro biotribological behavior of CFR-PEEK as bushings and flanges in a rotating hinge knee with articulation on zirconium nitride (ZrN) multilayer surface coating[37]. At physiologic contact stresses, the wear rate was more than 10 times less with CFR-

PEEK and ZrN compared to CFR-PEEK and CoCr. Given the significant metallic wear it was concluded that CFR-PEEK and CoCr should not be used in that combination as an articular surface[38]. The higher wear rates were attributed to the enhanced hardness properties of the CFR-PEEK material, but the ZrN was sufficiently harder to guard against increased wear. Similarly, Grupp et al. conducted an in vitro wear simulation to determine suitability of CFR-PEEK materials for fixed bearing unicompartmental knee arthroplasties (UKA) with low congruency. Wear rates between CFR-PEEK with two different carbon sources were not statistically different from one another but were high enough to conclude that they cannot be recommended for this application[39]. While the carbon fibers (diameter approximately 500 nm to 1000 nm) are cited as contributing to wear resistance of the composite material, the PEEK matrix could not be sufficiently protected during simulated walking.

Wear of the PEEK matrix in the prior studies may be related to the incomplete bonding of the matrix and the carbon fibers. Kyomoto et al. showed free radical production in PEEK under ultraviolet irradiation and the benzophenone (BP) units acted like photoinitiators that could control the "self-initiated" graft polymerization of poly(2-methacryloyloxyethyl phosphorylcholine) (PMPC)[40]. Nanometer-scale photoinduced grafting of PMPC on both CFR-PEEK and neat PEEK improved frictional properties, wear resistance, and water wettability of surfaces and interfaces[41]. The wear resistance of PMPC-grafted CFR-PEEK hip liners was then tested against metal and ceramic heads. Similar to the prior studies, the authors showed that that zirconia-toughened alumina (ZTA) femoral heads revealed a significantly smoother surface compared to CoCrMo femoral heads after the hip simulator wear test. Again, the carbon filler served as a surface hard enough to abrade cobalt alloys typically used in arthroplasty. PMPC-grafted CFR-PEEK is a promising acetabular liner material and especially when combined with a ZTA femoral head[42].

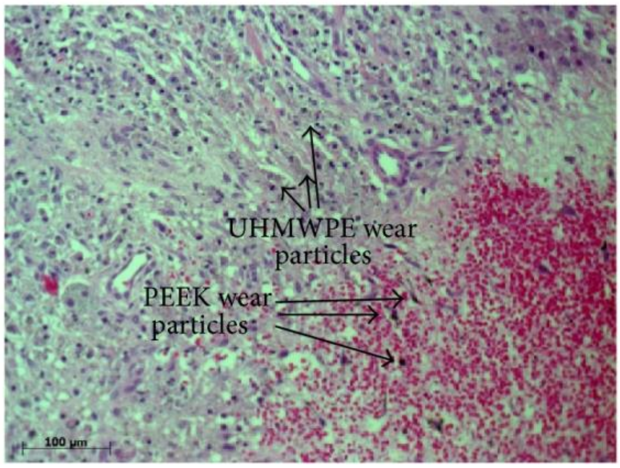

Fig. 3. UHMWPE and PEEK wear particles stained with hematoxylin and eosin, adapted from *BioMed Research International*[48].

Despite promising results from studies like Kyomoto's, the significant metallic wear in other studies[38], high wear rates in pin-on-disc tests[43] and an increased likelihood of delamination failure[44] suggest that CFR-PEEK is unlikely to see near-term use as a clinical bearing material in traditional articulation geometries.

Many studies have explored the immunological reaction of *in vivo* models to CFR-PEEK wear particles. Lorber et al. analyzed the biological activity from wear particles of CFR-PEEK pitch and pan compared to UHMWPE in synovial fluid, bone marrow and articular cartilage after injection into the joint[45]. There was an increased cytokine expression in adjacent bone marrow for both CFR-PEEK groups compared to UHMWPE and CFR-PEEK showed increased expression in articular cartilage. This resulted in proinflammatory potential of CFR-PEEK and was not recommended by the authors as a good alternative to UHMWPE for a bearing material. Grupp et al. also investigated *in vivo* biocompatibility with CFR-PEEK pitch and pan wear particles in mice to determine leukocyte or potential inflammatory tissue responses[46]. Synovial membrane thickening was caused after both CFR-PEEK were injected but no increased leukocyte activation or inflammatory tissue response compared to UHMWPE was seen. Another study showed similar results that CFR-PEEK wear particles did not increase the inflammatory response[47]. One study analyzed human synovial fluid with CFR-PEEK and UHMWPE wear debris in 10 patients undergoing rotating-hinge-knee implant revision surgery. CFR-PEEK was not the bearing material so there was a different wear mechanism that caused wear debris compared to the UHMWPE tibial insert. UHMWPE particles were scattered throughout the tissue while CFR-PEEK particles were agglomerated near various vessels but showed no giant-cell reactions (Fig 3)[48].

Rotating hinge knee implants have become a more common use for CFR-PEEK in arthroplasty. An in vitro study showed that both CFR-PEEK composites had high polymeric wear rate compared to neat PEEK and UHMWPE, and CFR-PEEK pitch fibers had the worst wear resistance[49]. However, CFR-PEEK has been used *in vivo* as flexion bushings and flanges and studies have followed various retrieval studies. Schierjott et al. examined the CFR-PEEK matrix worn out and fibers exposed both in vitro and in retrievals collected from revision surgeries[50]. However, EndRo, a new modular design using CFR-PEEK flanges and bushings resulted in good functional, radiologic, and clinical performances at a short-term follow-up[51]. Another study also showed positive results after looking at a longer-term clinical follow-up from complex primary and revision TKAs[52].

Outside of bearing materials CFR-PEEK has been indicated for structural applications including hip stems owing to a potentially better bone-implant compatibility and match in mechanical properties. Nakahara et al.[53] observed, in an *in vivo* study, there was no obvious damage in the retrieved CFR-PEEK stem but saw corrosion and fretting in other stems; the taper connection between the CFR-PEEK and ceramic head was more secure. Another *in vivo* model showed varying degrees of stress shielding on the hip stems and saw some bone ingrowth on the cementless cups[54]. Another study also saw stress shielding but concluded that a more flexible stem significantly lowers the stress shielding around the femoral bone[55].

Similarly, FEA testing of acetabular components in total hip arthroplasties largely concluded that CFR-PEEK could be a potential as both a shell and acetabular liner[31,56,57]. All studies appeared preliminary and cautioned that more testing was needed to make full conclusions about CFR-PEEK as an alternative to UHMWPE or conventional metallic shells. However, results from the previously reported knee studies suggest that wear studies of hip articulations will not be successful in the absence of a hard femoral head that is either all ceramic or coated in some way.

3.2.3 *High Density Polyethylene (HDPE)*

Although high density polyethylene (HDPE) is not common in arthroplasty surgeries given inferior mechanical and tribological properties compared to UHMWPE, some scientists have hypothesized that the mechanical and tribological properties could be optimized with the addition of nanoparticles. The most widespread nanoparticle added to HDPE has been nanographene. There are several advantages of these polymer composite materials over neat UHMWPE including: moldability, low density, high corrosion resistance and low cost[58]. The addition of graphene oxide powder to HDPE has exhibited improved wear and fatigue properties. All studies reviewed reported uniform distribution of the particles throughout the material up to 2.5 wt%, with little to no agglomerations observed. Additionally, these nanoparticles also act against bacteria, are biocompatible, and can be sustainably produced[58-60].

More recently, multi-walled carbon nanotubes have been added to HDPE and aluminum oxide to create a nanocomposite hip stem. The authors reported low cytotoxicity, and increased hardness with the inclusion of carbon nanotubes[61]. In addition, nanoparticles added to polyethylene utilized in shoulder joint arthroplasty to create bio-composite materials, are also being studied with a rationale that these materials could improve soft tissue healing[62].

3.2.4 *Ultra High Molecular Weight Polyethylene*

UHMWPE is currently the most used articular surface material for all joint arthroplasties. Carbon fibers have previously been combined with UHMWPE with detrimental results attributed to poor matrix integration, oxidation and subsequent release of fibers[63]. Nanoparticles, most commonly multi- and single-walled carbon nanotubes, have been added to UHMWPE with the intention to improve tribological and mechanical properties. Other additives consist of biocompatible epoxies, chopped carbon fiber and alumina.

Single-walled carbon nanotubes (SWCNT) have been investigated for arthroplasty application in combination with UHMWPE due to reported biocompatibility, corrosion resistance, and low wear debris. One study examined functionalized SWCNT-UHMWPE composite manufacturing and mechanical properties for the use in unicompartmental knee arthroplasty[64]. Two composites were developed to enhance biocompatibility and mechanical properties when using single-point incremental forming process (SPIF) to manufacture unicompartmental knees. These composites had improved tensile properties, maintained 90% osteoblast viability, and promoted osteogenic differentiation more than neat[64].

Multi-walled carbon nanotubes (MWCNT) were used in one study to compare wear properties and biocompatibility against neat and cross-linked UHMWPE[65]. The MWCNT-UHMWPE composite was comparable in wear resistance to cross-linked UHMWPE and to non-cross-linked UHMWPE in terms of impact resistance. The composite also showed no adverse biological effects and complied with requirements of biosafety testing. An additional study looked at the potential for a MWCNT-UHMWPE composite as a piezoresistive sensing material[66]. An analytical model was built to estimate the ideal depth from the tibio-femoral contact surface where an embedded sensor could attain the highest stress resolution and smallest distortion energy. The results showed resistance of MWCNT-UHMWPE composites exponentially decreased under applied stress and could be used as a piezoresistive sensing material.

Carbon fibers mixed into UHMWPE were investigated to understand the impact of the composite in lowering stress intensities and specific wear rates. Ramesh et al. used FEA to look at the design of flexion angle and sagittal radius of a tibial insert for prosthetic knees[67]. The goal was to minimize stresses at knee interfaces through chopped carbon fiber integration to ensure high performance knee joints. It was found that alumina ceramic and UHMWPE-chopped carbon fiber combination had the lowest stress levels of the different variations. Additionally, Baliga et al. studied the synthesis and wear characterization of UHMWPE-carbon nanofiber (CNF) composites[68]. This showed composites mixed with paraffin processing improved the distribution of CNFs and lowered the specific wear rate compared to neat UHMWPE but not significant enough yet to be a competitor against the standard cross-linked polyethylene.

Ceramic-UHMWPE nanocomposites show promise in laboratory tests. UHMWPE-Al_2O_3 with 3 wt% Al_2O_3 (20 nm) was compared to neat UHMWPE and UHMWPE-Al_2O_3 after mechanical activation in a ball mill for potential use for damaged cartilage replacement[69]. Mechanical properties such as compression and wear resistance were tested. UHMWPE-Al_2O_3 after activation showed improved mechanical properties, attributed to better interactions of the nanoparticles with the polymer matrix after mechanical treatment. UHMWPE-Al_2O_3 after activation was then implanted in rats which showed no signs of inflammation, cellular infiltration destruction of the material or bone-cartilage defects.

3.2.5 *Polyamide*

Beyond bearing surfaces, composite materials are of interest in joint arthroplasty due to the ability to tune mechanical properties to be closer to bone than neat polymers or monolithic metals. One of the largest concerns with replacing a joint surface with high modulus materials is stress shielding of the underlying bone, leading to bone resorption and potentially mechanical failure. The suitability of polyamide in combination with carbon fiber as a support structure has been studied in a few computational models. These studies concluded that indeed the composite implants reduced stress shielding compared to their metal counterparts, which would theoretically lead to less bone loss over time[70,71]. The carbon fibers serve to create a more biomimetic implant, which is hypothesized to facilitate the load transfer at the bone implant interface, and therefore reduce bone loss. Interestingly, one computational study found that there was more dense trabeculae near the implant when using a composite stem compared to both cobalt-chromium and titanium alloy stems[72]. However, dynamic loading conditions will require further studies to ensure that the carbon fibers can also prevent fatigue crack propagation rather than provide pathways for crack travel along poorly integrated fibers.

3.3. *Ceramics*

Ceramic materials have long been utilized in arthroplasty surgeries, particularly as femoral heads in THA surgery and some femoral components in TKA surgery. The wettability and compression strength of ceramics make them well suited to serve as highly loaded bearings. Importantly, the high hardness of ceramics allow for creation of a durable surface with very low roughness. The surface itself doesn't wear, and when articulated against polymer bearings, it produces less wear particles, making it less likely to manifest osteolysis *in vivo*[73].

Early ceramics demonstrated an increased risk of fracture *in vivo*, due in part to their decreased toughness in comparison to metals[74]. For nearly two decades the most common ceramic in use in the United States has been an yttrium stabilized, zirconia toughened alumina incorporating chromium/strontium oxide nanoparticles for additional resistance to crack propagation. More recently, different nanoparticles have been added to ceramic materials to further improve their biocompatibility and fracture toughness. Several studies have demonstrated decreased cytotoxicity and increased mechanical properties with the adjunct of these nanoparticles including zinc oxide and graphene[75-77]. A few studies have also explored the processing of ceramic nano-materials including rapid sintering and CO_2 laser co-vaporization[78,79]. The theoretical hardness increase associated with the Hall-Petch relationship does not appear to be limited by increased brittleness owing to the nanomaterials ability to prevent crack propagation.

3.4. *Other/Metals*

For decades most of the THA and TKA components that interact with bone (tibia and femur), have been made of titanium or cobalt alloys. Using nanoparticles to decrease the modulus of these metals could potentially reduce the aforementioned stress shielding and improve biocompatibility. For instance, composite hip stems combining a titanium alloy with carbon fiber exhibited good results at 10 years post-op in a randomized clinical trial in Northern Ireland[80]. The authors analyzed bone mineral density and found patients with the composite stem had retained more proximal femoral bone stock compared to the metal stem group. The carbon fibers serve to provide appropriate toughness to the otherwise notch-sensitive titanium. The addition of a graphene coating on titanium implants has also been explored to improve biocompatibility although the pathway of how graphene affects bone marrow cells warrants further investigation[81].

3.5 *Biocompatibility Concerns*

This review focused on the mechanical, tribological, antibiotic, and lubrication properties of nanoparticles in arthroplasties, however, biocompatibility is of paramount concern when considering implantation of these materials. By design, this review focused on intentional incorporation of nanoparticles into materials rather than their generation through wear or failure of a device. The biological impact of these unintentional particles on the human host are well characterized. However, most of the papers included in the review focused on material properties without considering cytotoxicity, endotoxicity, carcinogenicity and teratogenicity.

Nonetheless, several reviewed articles did include biocompatibility tests as discussed in each section and summarized here. For coatings and lubricants, several of the studies included in this section examined a combination of cellular toxicity, cellular behavior and/or biofilm resistance as it related to the nanoparticles of interest[8,10,11,14,19-22,25,81]. Additionally, a few of the articles dealing with nanoparticle additives to bone cement also addressed biocompatibility or antibacterial properties utilizing *in vitro* studies[27,29]. Fouad et al. evaluated the cytotoxicity of graphite nanoparticles added to HDPE[60]. Finally, for nanoparticle additives to ceramics, a few articles analyzed cytotoxicity[77] and *in vitro* biocompatibility[76,82]. As discussed in 3.2.2, CFR-PEEK composite biocompatibility has been investigated through various *in vivo* studies. Lorber et al. discussed the cytotoxicity in the synovial joint fluid, bone marrow, and articular cartilage[45]. CFR-PEEK and UHMWPE particles have been injected as whole particles as well as wear particulates after an *in vivo* study has been completed[45-52]. To create a more holistic investigation, long-term carcinogenicity and endotoxicity studies must be completed. Additionally, degradation and the subsequent excretion pathways by which these nanoparticles are excised warrants further investigation.

In support of this work, an additional search for review articles concerning biocompatibility in the orthopedic space netted no new articles. However, biocompatibility of individual nanoparticles, not composites, were found. Carbon nanotube biocompatibility has been reviewed by Aoki et al. and while there have been questions raised around possible carcinogenicity, there has been no clear evidence of neoplasms in mouse models other than inconclusive results with inhalation studies[83]. Similar to conclusions around biocompatibility in this review, varying results have been reported in other reviews and a continuation of such work must be performed before this nanotechnology could be employed in clinical settings. At larger scale, carbon in fiber form in orthopedics has been reported to exhibit good biocompatibility while the mechanical properties are still not matched for intended applications[84]. Overall we conclude that the biological aspects of nanotechnology in knee and hip arthroplasty is insufficiently studied and reported.

4. *Discussion*

An aging population and increased acceptance of joint replacement as an early intervention for joint pain has led to a significant increase in the number of TKA and THA surgeries worldwide. More medical devices implanted at earlier life stages will require improvements in implant material durability realized through innovation in materials science. Nanoparticles are one avenue that have shown promise in several preliminary studies, although more holistic studies are needed prior to these technologies being adopted systematically. While no one material appears ready for clinical implementation, the present review reveals carbon additives to be at the forefront of the field. Multiple approaches showing promise appear to result in reduction in stress shielding, increased osteointegration, and the potential to reduce wear. The current literature review reveals that significantly more research should be performed before these materials can be advanced to human trials.

Despite the knowledge base incorporated in this review, scientific gaps remain. *In vivo* experiments, in animals and particularly in humans, are frequently referenced as the next necessary step of progression. Along with *in vivo* studies, the literature base is deficient with respect to (1) the impact of nanocarbon particles on bacterial infections, (2) expansion of FEA model parameters to address inclusion of nano- and micro-scale interactions in composites, and (3) experimental validation. Additionally, while the focus of most manuscripts is knee and hip arthroplasty on account of their significant market share and societal expense, shoulder and ankle arthroplasty procedures are increasing in frequency but have different load and motion patterns than other joints. Biomaterials research for these applications is less mature and warrants more investigation.

4.1. *Limitations*

This study is not without limitations. First, this review was limited to investigating nanoparticles in joint replacement. This particular search strategy required cited materials to identify potential applications of a technology to joint arthroplasty. It is acknowledged that some materials at earlier technology readiness levels may well be positioned for use in human joints but not yet identified as such in the literature base. Further, because arthroplasty was specified, studies examining nanoparticles in joints, but related to ligaments, cartilage repair, or tissue regeneration were excluded. While studies investigating nanoparticles generated as wear debris were excluded, the authors recognize this is a large field of important research with potential to inform biological reaction to nanoparticles evolved from biomaterials outside of wear mechanisms. During the investigation into biocompatibility, holistic review articles on nano-composite materials in orthopedics were lacking or outdated. Finally, nanoparticles for drug delivery applications were also not included.

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