SECTION VI

SUMMARY OF TESTING

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This section contains a survey of published reports on the testing of modern metal/metal hip implant designs and a summary of the biocompatibility issues related to metal/metal hip bearings. A comprehensive reference list is provided in Appendix 2.

Introduction

Metal/metal femoral head-acetabular cup combinations were originally introduced in the 1960s with implants such as the McKee-Farrar, Ring, Stanmore, Sivash, and Muller prostheses. The success of these *first generation* metal/metal devices, however, was limited by a poor understanding of the design issues of metal/metal technology and limitations of the manufacturing process used to make these parts. These first generation metal/metal devices were often characterized by problematic outcomes including equatorial contact caused by low or negative head-cup clearances and deformation of thin-shell acetabular cups, both of which resulted in high frictional torques, component seizing, and implant loosening.[139,185,189,192]

It is clear, however, that the problems undermining the clinical success of the first generation metal/metal joints resulted primarily from suboptimum implant design and manufacture. It is important to note that these problems were not related to the wear performance of the metal/metal bearing combination itself. Indeed, many of the early metal/metal implants have survived *in situ* for over two decades,[139,189] and there have been only few documented reports of associated problems with peri-implant osteolysis (which were deemed to be related to polymethylmethacrylate particles, not metal particles).[24,58,75,185] Furthermore, analyses of retrieved metal/metal components after long service periods typically indicate highly polished surfaces with minimal scratches, near maintenance of the original surface finish,[34,39,40,59,61,75,138,185] and relatively low linear and volumetric wear.[34,132,138,139,189,190,191]

Although the majority of total hip implants used in North America over the past three decades has involved metal head on polyethylene cup articulating couples, the recent consensus in the orthopaedic community that polyethylene particles are the primary cause of peri-implant osteolysis has led to a revived interest in metal/metal technology. Metal/metal implants have been shown in both retrieval and laboratory studies to experience up to two orders of magnitude less wear compared with conventional metal/polyethylene implants.[61,80,106,108,118-120,128,133-135,138] From the standpoint of reducing the volume of wear particles generated, the use of metal/metal implants may provide tremendous clinical benefit.

For metal/metal implants to represent a viable alternative to conventional metal/polyethylene systems, the identification of the design and manufacturing issues for metal/metal technology is crucial. To achieve this, the orthopaedic community has moved forward through concerted research efforts to understand the salient engineering issues in order to optimize metal/metal bearings for use in total hip arthroplasty.

Much of the recent work published in the orthopaedic literature has focused on the design parameters that control the wear of metal/metal hip implants with the following major conclusions.

Design Issues

1. Material

Metal-metal implants have been traditionally fabricated from surgical grade cobalt-chromium-molybdenum (CoCrMo) alloys because of their corrosion and wear resistance. They are generally well-suited as self-bearing materials and are known for a specific *self-healing* capacity where visible surface scratches are typically polished out rather than made progressively worse with continued cycles in service.[122,124,141,142] This is an essential property in light of the possibility of entrapment of third body wear particles (metal or acrylic) or release of hard carbide phases of certain CoCrMo alloys into the articulating interface during service.[141,142]

Both cast and wrought forms of CoCrMo have been used clinically with reasonable success.[69,185] Although many engineering details about first generation metal-metal hip implants were largely undocumented (or undisclosed), it is known that the original McKee-Farrar implants were made from the cast material. The wrought alloy, on the other hand, is available with varying levels of carbon with nominal levels of < 0.05 % and > 0.25 % carbon for low and high carbon alloys, respectively. With differing levels of carbon content, the relative wear resistance of either wrought CoCrMo has been the subject of experimental scrutiny.[69,89,91,133-135] Wrought alloys in general have also been shown to exhibit lower friction in pendulum studies.[69,133-135] Streicher et al[69,135] have suggested that high carbon wrought rather than cast CoCrMo alloys has superior wear performance based on pin-on-disc wear testing with a very high contact stress. This behaviour may have resulted from the presence of small, finely distributed carbides at the component surface rather than the coarse, more widely spaced carbides of the cast alloy.[69,133-135] The smaller carbides and smaller grain sizes of the wrought material generally result in reduced surface roughness and increased hardness thus enhancing mechanical properties. Because the low carbon grade of wrought CoCrMo alloy does not have pronounced carbides at the surface, even lower surface roughness can be achieved. In terms of wear performance, however, the benefits of decreased surface roughness may be compromised by the slight decrease in bulk hardness of the low carbon wrought material.[69,133-135] However, recent laboratory evaluations using sophisticated hip simulators have indicated that both cast and wrought forms of CoCrMo, with the wrought material in both low and high carbon formats, exhibit similar wear properties.[89,91] It is important to note that this was the case when other design variables (to be discussed) were held relatively constant, suggesting that wear performance is less sensitive to the particular grade of CoCrMo alloy when other specific engineering parameters are well-controlled within specific limits.

2. Clearance

To avoid problems related to high frictional torques and equatorial seizing associated with first generation metal/metal implants from the 1960s, the current approach is to provide a small gap or *clearance* between the femoral head and acetabular cup components. This ensures a *polar* contact, where the head-cup contact area is necessarily placed away from the equator.[136,139]

Suggestions have been made that an optimal range of clearance values (mismatch between the major head and cup diameters) exists for metal/metal articulations with lower clearances favorable for improved wear performance.[61,69,133,135] This has been confirmed in recent studies where head-cup clearance was identified as an independent parameter affecting metal/metal wear performance.[84-91,93,94,97-100,107,130] In spite of this work, the optimum clearance may not be the lowest possible mismatch that can be manufactured. Extremely small clearances can result in off-the-shelf parts to be matched with an excessively tight fit, thus resulting in congruent head-cup components and potentially resulting in the equatorial contact that plagued the original first generation designs. Furthermore, tight clearances can also prevent the ingress of lubricant and egress of wear particles. Therefore, the optimum design clearances must be a combination of low clearance to achieve low wear and high enough clearance to meet design safety.[84-91,93,94,97-100]

3. Form and Finish

With the availability of both improved manufacturing processes and sophisticated metrology devices used for quality assurance, head and cup components can be manufactured with high quality surfaces and form (sphericity). Much of the recent metal/metal testing has been performed on parts that have been finished on several commercially-available final-stage grinding units that can achieve extremely good sphericity and low surface roughness values.

Form has not been specifically quantified as a parameter affecting metal/metal wear. However, it has been suggested that the initial period of slightly accelerated wear (often referred to as the *wear-in* or *bedding-in* phase) is the correction of initial asphericity between the head and cup components. Better sphericity may therefore result in a more gentle wear-in phase and thus a lower amount of total wear.[89,90,100]

Surface roughness, however, has been identified as a variable that can modulate the wear performance of metal/metal parts. Simulator studies have shown that wear decreases with lower starting surface roughness values.[84-91,93,94,97-100] This is particularly important as femoral head surface roughness has not been identified in the literature as a critical design parameter affecting metal/polyethylene wear. Manufacturers, therefore, must try to achieve lower surface roughness for both the head and cup components of a metal/metal bearing through advanced grinding and polishing technologies.

4. Lubrication

In first generation metal/metal implants, a type of lubrication referred to as *boundary lubrication* was thought to have occurred where molecular components of the lubricant would bond chemically to the metal head and cup surfaces. The adherent lubricant layer would shear in preference to the surfaces themselves, thus providing some degree of surface protection during articulation.[136-138]

Whilst it would be difficult to achieve full *fluid film lubrication* where a microscopic layer of lubricant would completely separate the head and cup surfaces in relative motion, some degree of lubrication may be expected. Theoretical studies employing advanced lubrication theory have indicated that strict control over design and manufacturing can, in fact, produce conditions favorable for fluid film lubrication to occur.[92,100,109] Specifically, low clearance values can result in larger head-cup contact areas and the corresponding generation of thicker lubricant film layers at the articulating interface.[92,100] Furthermore, lower surface roughness values have also been shown theoretically to result in a more effective lubricant layer (because rough counterface surfaces would require a thicker lubricant layer for complete separation compared with smooth surfaces which can be separated by thinner lubricant layers), thus enhancing the state of lubrication between the articulating surfaces.[92,100] In fact, a time-varying lubrication model was developed that suggested that sufficiently low clearance and low surface roughness can result in good fluid film lubrication of metal/metal implants even under the varying loads experienced in service due to normal gait.[92,100] It should be emphasized that these studies were theoretical analyses based on established lubrication theories that have been proven for other engineering fields. However, of note is a recent study which provided direct experimental evidence of lubrication for metal/metal hip implants tested on a hip simulator.[103] This work is important because it corroborates the previous theoretical studies indicating that the protection of metal/metal articulating surfaces is possible through an interposed fluid layer and that lubrication is a major mechanism in the wear reduction of metal/metal bearings. Coupled with theoretical lubrication studies and the extensive database of published wear test results for metal/metal hips, low wear can be achieved when specific major design parameters are properly controlled.

Simulator Issues

All modern evaluations of metal/metal implants have been performed using simulators that subject the test specimens to close-to physiological load levels and motion. Because these tests are simulations, it is important to determine how closely they represent in vivo wear morphology. For metal/metal implants, Park et al[122] compared the morphology of wear produced in several types of hip simulators from different laboratories to what has been observed on retrieved metal/metal implants. Allowing for differences in the location of the wear zones, a result of specific kinematics unique to each machine, the types of wear appeared very similar amongst the machines. Perhaps of greater importance is that the types of wear were also found to be very similar to what was seen on the retrieved modern metal/metal hip bearings examined in the same study.

From a wear particle standpoint, Campbell et al[150] examined the histological appearance of tissue around retrieved metal/metal hip implants to characterize metal wear particles. They found that particles were relatively small (< 200 nm) with the majority of particles described as amorphous with undefined edges (i.e. oval or round). The particle morphology from Campbell et al[150] was confirmed in a similar study by Catelas et al[152] in which the majority of particles extracted from the serum of simulator-tested metal/metal hip implants was identified as either round or oval and less than approximately 233 nm in size. It is encouraging, therefore, that existing metal/metal simulator studies have produced results that correlate well with clinical data, indicating that hip wear simulators are viable tools for evaluating wear performance.

Biological Issues

A significant amount of research has been performed using animal and biologic models to assess the biological response to metal implants. These articles explain the level of metal particles/ions released, the nature of any reactions, where these particles eventually reside, how they are able to move within the system, and long term effects.

1. Particles and Inflammatory Response

Doorn et al[155] and Amstutz et al[183] presented reviews of histologic reaction to metal versus polyethylene wear in total hip replacements. Polyethylene particles were found to generate a cellular response consisting of mononuclear histiocytes and multinucleate foreign body cells; metal wear particles generated a reaction of mononuclear histiocytes with rare giant cells.

Doorn et al[157] analyzed four long term McKee-Farrar (21-25 years) implants and five short term metal/metal implants (<2.5 years) of various designs. Metal particle sizes ranged from submicrometre to 1-4 μm. Generally, the metal debris did not invoke production of multinucleate giant cells as had been previously seen with polyethylene implants, most likely due to differences in size and number of particles. The lower volumetric wear (10-40 times less) with metal/metal as compared with metal/polyethylene is significant with respect to the lower amount of histiocytic reaction seen. Doorn reported that the distribution of the histiocytes reflected the initial pathway of the metal particles. After being ingested along the synovial surface, particles were transported to lymph or deeper soft tissues. These findings were also supported by Brodner et al[148] and Jacobs et al[165] who found elevated levels of serum cobalt and serum chromium. If transport of particles via the lymph system was less than the locally produced amount, histiocytes should eventually fill the periprosthetic tissue. If an excess amount of metal particles is generated, local tissue buildup could occur with possible harmful response to the bone/implant interfaces. However, if wear generation was not excessive, equilibrium and histiocytic activity could be maintained within the periprosthetic tissue.

Campbell et al[150] examined the histological appearance of tissue around retrieved metal/metal hip implants and determined the biological response to particles. They found that there were fewer macrophages and wear particles in these tissues compared with typical samples from metal/polyethylene hips. In general, the macrophage and giant cell response to particles from metal/metal articulations was described as "mild".

Willert at al[182] evaluated 19 retrieved metal/metal devices as well as the surrounding tissues. Chromium was found in the greatest proportion followed by cobalt, nickel and molybdenum. Although the ratio of chromium to cobalt in the initial material was reported to be 0.5 to 1, tissue analysis revealed a significant shift (10 to 18 times higher) towards chromium. Tissues surrounding the retrievals were not dominated histologically by metal particles as very little particulate wear was found. Similar to the work of Doorn et al[157], particle size ranged from 0.5 to 5 μm. Even more similar is the fact that particles were also found around blood vessels, indicating transport via the perivascular lymphatics, which has also been suggested by Doorn[157].

Langkamer[168] , like Willert[182] and Doorn[157], presented a review of systemic wear debris in two total hip retrieval cases (titanium hip implant, Charnley stainless steel hip implant). Tissue analysis revealed that chromium levels increased to a ten fold level in the synovium, bursa and lymph nodes. Although widespread particle dissemination was found in the nodes, spleen and liver, concentrations were highest in the synovium and tapered off into these more distant organs. This report confirmed that particles move via the lymphatic system.

2. Toxicity

Merritt et al[171] reported on the distribution of metal products and the associated biologic reactions. The majority of materials from which orthopedic devices are manufactured (cobalt, nickel, molybdenum) were rapidly cleared from the body in urine. Chromium^{+3} (the same valence as nutritional supplements) was less toxic to cells while the Cr^{+6} state was shown to become cell-associated and highly toxic. This form is unlikely to occur in the use of metallic implants. Studies involving CoCr injections have shown that there is initial cell toxicity as corrosion begins, but that normalization occurs once the particles are completely corroded to the ionic state and removed.

Howie et al[164] noted that cellular models showed that once phagocytosed, the metal oxides of CoCr particles were disrupted by the reduction in pH, causing release of cobalt ions. These Co^{+2} ions, which were more stable at neutral pH, were suggested to be toxic to cells. Chromium in the Cr^{+3} form, on the other hand, was more stable at neutral pH because it could not cross cell membranes as could Cr^{+6} ions (highly toxic). Studies to date have shown no formation of the Cr^{+6} ions from solid implant materials. Howie also reported that intra-articular injection studies in rats revealed that exocytosed cobalt (from digested CoCr) at cell death seemed to lessen particle toxicity to other cells. This was confirmed by presence of early macrophage cell death followed by the appearance of healthy macrophages containing endocytosed material. Howie warned that animal models may not be fully representative of human responses since single bolus delivery is often used (instead of over time) and animal sensitivity may be at question.

3. Hypersensitivity

Evans et al[158] analyzed 39 patients with uninfected CoCr components. and suggested an association between loosening and sensitivity to the metal alloy. Metal sensitivity tests revealed that in cases in which the component was loose, nine showed metal sensitivity whilst five did not. Of 24 cases in which there was no looseness, no metal sensitivity was detected. The correlation between loosening and sensitivity was not statistically relevant and there have been no additional studies to date expressing this relationship.

4. Carcinogenicity

Howie et al[164] reported that particulate CoCr in animal models, whilst still associated with macrophages, had shown a doubtful link to tumor formation. Chromium in the Cr^{+3} form, which is more stable at neutral pH, is not able to cross cell membranes as is the case with the extremely toxic Cr^{+6} ions. Studies to date have shown no formation of the Cr^{+6} ions from solid implant materials.

Lewis et al[169] presented results of rats injected intraarticularly with wear particles 1.5 to 50 µm in size and examined over a two year period. CoCr particles were generated in a wear simulator. Positive (nickel subsulfide) and negative (manganese) controls were also used. Those rats receiving CoCr particles had no local tumors. Particles were identified in the subsynovium with minimal fibrosis. The author offered that a significantly larger group (500 rats) would be needed to substantiate a 1% tumor incidence.

Swanson et al[175] pointed out that although his wear and laboratory studies in rats did tend to indicate that CoCr particles constitute a risk of carcinogenesis, the risk is extremely small and not calculable. Additionally, the probable induction period is longer than the life expectation of many patients who could potentially benefit from such operations. As an interesting comparison, Swanson noted that earlier rat studies on larger particle polyethylene generated this same conclusion (carcinogenesis).

Case et al[153] analyzed the genetic aberration (chromatid breaks, gaps, etc.) in the marrow samples of 71 revision arthroplasty patients and 30 primary arthroplasty patients. Revisions included 27 Charnley devices, 17 D-series, 5 Howse, 6 Thompson, 1 each of Harris-Galante, Wagner, Stanmore, and Exeter, 3 unknown, and 2 each of McKee-Farrar and Ring prostheses. Case found that aberration was higher (statistically significant) in marrow cells adjacent to stems in revision cases than in marrow of the iliac crest of the same patient or in patients undergoing primary arthroplasty. These findings are significant since the majority of the revision cases were "standard" arthroplasty devices and not metal/metal devices.

Visuri et al[178] reported on 433 cemented McKee-Farrar patients (511 devices) operated on from 1967 to 1973 representing 5729 person years. Average follow-up was 9.2 years for males and 9.8 years for females. Using the Finnish cancer registry, it was found that the risk of total cancer of THR patients did not increase. However, the incidence of site specific cancers did vary. A decreased risk of breast cancer was found. A slightly increased risk of leukemia and lymphoma was also found. The author cited other published reports supporting the fact that while cobalt has carcinogenic properties, there was inadequate evidence to show that it is a human carcinogen. Cobalt has reportedly been used for more than 20 years as an anemia treatment since it stimulates erythropoeisis; no cases of cancer have been reported. Longer term studies with more patients were recommended to allow further analysis.

As a follow-up to his prior work focusing on McKee-Farrar implants[178], Visuri[179] compared the incidence of cancer in both metal-on-metal and metal-on-polyethylene devices to that of the general population in Finland. Again using the registries available, a significant amount of follow-up (over 28,000 person years) over a long period of time (12.5 years for metal/polyethylene, 15.7 years for metal/metal) was assessed. Both groups were found to have significantly less occurrence of lung cancer and no variation in the rate of other cancers when compared to the general population. Metal-on-metal patients had an insignificantly (i.e., not statistically significant) increased risk of leukemia and lymphoma. No local sarcomas were noted in either group. The overall cancer rate for metal/metal patients was lower than that of the general population in all but the 12th year (examined over a 15 year period). Based on the information, it is suggested that factors other than the total hip arthroplasty played a major role in the origin of cancer. In a more recent study describing a longer follow-up, Visuri[177] was unable to confirm the previously described increased risk of leukemia and lymphoma. Furthermore, lung cancer and the risk for cancer mortality were reduced and the risk of local sarcoma was insignificant.

Tharani et al[176] concluded in their analysis that there was no causal link between total hip replacement and cancer, and that there was only one study in which there appeared to be an increased risk of cancer following metal/metal total hip replacement but that this was small in comparison with other studies. Their review also showed no increase in bilateral patients which is another observation against cancer induction by total hip arthroplasty.

Gillespie et al[159] presented results from an analysis of 1358 total hip patients (representing 14256 person years) in New Zealand from 1966 to 1973. Mean follow-up was 10.52 years (6 months to 17 years). Similar to the works of Visuri[177-179], cancer and death registries were searched for this same time period; 164 cancers were recorded. Overall incidence of cancer following THR was significantly decreased through 10 years. Overall incidence significantly increased for patients followed beyond 10 years. Breast, colon and rectal cancer was significantly diminished in THR patient to 10 years. Lymphatic and hematopoietic cancers were found to be significantly increased overall in THR patients. The author notes that these associations may be purely mathematical chance or related to other underlying factors such as concomitant disease treatment or social/occupational factors (e.g., pesticides in agrarian New Zealand).

Mathiesen et al[170] presented an analysis of 10785 total hip patients in Sweden (representing 58437 patient years) implanted from 1974 to 1988. Use of the Swedish cancer registry and death registry allowed evaluation of tumor incidence. The overall actual incidence of malignancy (881) was lower than expected (917.7). Incidence of leukemia and lymphoma was slightly higher in the first year of follow-up but had a corresponding decrease the second year of follow-up. When year 1 and 2 are analyzed together, this incidence is not significant. Patients followed for greater than 10 years had a slightly higher incidence of total cancer, but a decreased risk of leukemia and lymphoma. Bilateral and revision patients were analyzed as a subset in order to evaluate potential for increased malignancy due to increased exposure. The overall cancer incidence in this subset was found to be less than expected for bilateral patients and slightly increased for revision cases; leukemias and lymphomas were less frequent than the entire series. Possible selection bias is cited as THR patients are generally more healthy with a longer life expectancy. The author notes that an association between THR and increased incidence of cancer during the first 10 postoperative years was unable to be made, possibly due to the long latency period for metal associated cancers.

5. Summary

- Metallic wear particles result in a cellular reaction consisting mostly of mononuclear histiocytes, which differs from that seen with polymer particles (mononuclear histiocytes and multinucleate giant cells).
- Metal/metal bearings can result in increased serum and urine metal (cobalt, chromium) ion levels
- Cobalt ions are initially toxic to cell tissues but may be normalized after clearance. Chromium ions appear to be toxic only in the hexavalent state which has not been shown to occur with metal implants.
- Wear particles from metal/metal couples tend to be extremely small (submicrometre to 5 μm).
- Concentrations of metallic wear particles are typically highest in the immediate surrounding tissue (e.g., synovium) with concentrations tapering off at more distant organs supplied by the lymphatic system and blood. Organs which perform a processing/filtration function (e.g., liver, lymph nodes) experience increases in metal levels over the normal.
- Cancer/tumor studies have shown no correlation or extremely small and unmeasurable correlation with the presence of CoCr wear particles.
- Analyses of massive patient registries in three countries (New Zealand, Finland, Sweden) have been unable to make a strong statistically significant link between cancer incidence and total joint arthroplasty. Although several articles have shown a slight increase in risk of leukemia and lymphoma for total hip replacement patients, many also report that incidence of other cancers have shown a decrease when correlated to total joint replacement. These authors suggest that factors other than total joint replacement may play a role in cancer formation.

Overall Summary

In light of the potential for improved wear performance of metal/metal hip bearings, extensive effort has been undertaken in the late 1990s to identify the major parameters affecting wear. Modern studies have been successful in providing the community with credible information on the key engineering issues of metal/metal implants from the perspective of improving wear performance. Advances in manufacturing technology have also provided the industry with methods to consistently fabricate implants to specific design criteria. It is fortuitous that parameters identified as key influences on wear performance are directly controlled by careful engineering and modern manufacturing. Furthermore, extensive research has provided experimental validation that metal/metal implants can achieve low wear in a reproducible fashion and under clinically relevant conditions. Whilst the biological response to metal particles and ions remains a topic for scientific scrutiny, metal/metal bearings has been shown both experimentally and clinically to result in several orders of magnitude less wear compared with conventional metal/polyethylene implants. Therefore, there is potential that their use may mitigate the problem of wear particle-induced osteolysis in total hip arthroplasty.