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--Chief Editor

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L. Nordsletten⁹, R. Lappalainen¹⁰, W. Jiranek¹¹, S.B. Goodman¹²,
E. Gomez-Barrena¹³, K.D. Draenert¹⁴, P. Aspenberg¹⁵.¹Department of Medicine, Helsinki University Central Hospital, Helsinki, Finland ²ORTON Orthopaedic Hospital of the Invalid Foundation, Helsinki, Finland ³COXA Hospital for Joint Replacement, Tampere, Finland, ⁴Hospital for Special Surgery, Biomechanics, New York, NY, USA, ⁵Orthopedic Hospital Valdoltra, Ankarana, Slovenia, ⁶Department of Orthopaedics, Yamagata University School of Medicine, Yamagata, Japan, ⁷Technion-Israel Institute of Technology, Haifa, Israel, ⁸Department of Orthopaedics and Traumatology, Helsinki University Central Hospital, Helsinki, Finland, ⁹Zimmer Europe GmbH, Winterthur, Switzerland, ¹⁰Bone Bioengineering Group, Center for Orthopedic Research, Lausanne, Switzerland, ¹¹Orthopaedic Centre, Ullevål University Hospital, Oslo, Norway, ¹²Department of Physics, University of Kuopio, Kuopio, Finland, ¹³Department of Orthopaedic Surgery, Virginia Commonwealth University, Richmond, Virginia, USA, ¹⁴Department of Orthopaedic Surgery, Stanford University Medical Center, Stanford, California, USA, ¹⁵Department of Orthopaedic Surgery, Fundación "Jiménez Díaz" Hospital, Madrid, Spain, ¹⁴Zentrum für Orthopädische Wissenschaften, München, Germany, and ¹⁵Department of Orthopaedics, Linköping University Hospital, Sweden.*case reports & studies*Exacerbation of rheumatoid arthritis following *Helicobacter pylori* eradication: disruption of established oral tolerance against heat shock protein? 103

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Total joint replacement and aseptic loosening

Y.T. Konttinen¹, T.M. Wright², R. Trebse³, M. Takagi⁴, M. Silbermann⁵, J. Salo⁶, C. Rieker⁷, D.P. Pioletti⁸, T. Ogino⁴, L. Nordsletten⁹, R. Lappalainen¹⁰, W. Jiranek¹¹, S.B. Goodman¹², E. Gomez-Barrena¹³, K.D. Draenert¹⁴, P. Aspenberg¹⁵

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AUTHORS' SUMMARY

Total joint replacement reproduces a near normal joint function. Laminar flow, operation theatres, intravenous preoperative antibiotics and use of antibiotic cements decrease immediate and late infections. Improved implant biomaterial, surface finish and coating, and design and implant modularity, together with modern cementing and optimal surgical techniques, help ensure proper positioning of the implants. Long-term problems may be related to wear particles (which can be minimized with the use of hard-on-hard articulations or with highly cross-linked ultra-high molecular weight polyethylene), delayed type hypersensitivity, infections and/or poor initial fixation as a result of postoperative nonsteroidal anti-inflammatory drugs (NSAIDs) use. Peri-implant bone resorption can be decreased with the use of bisphosphonates. Greater than 90% success rates can be achieved in the long term with joint replacement.

Biomechanical load

Appropriate loading usually strengthens tissues, whereas insufficient loads lead to disuse atrophy, and excessive loads to damage and inflammation. This may not hold true for the interaction between bone tissue and joint implants. Experience from dental implant surgery suggests that optimal fixation might be obtained if the implant could initially

remain unloaded to minimize interfacial motion and the formation of a fibrous capsule formation. In total joint replacement surgery this has not been proven and is a matter of discussion. Furthermore, maximizing integration by postoperatively unloading joint replacement components cannot be achieved for practical reasons of rehabilitation and mobilization, although research and development in this direction is ongoing.

Solid, permanent overall osseofixation is only an illusion. The high cyclic loading that occurs with activities of daily living and the mismatch in mechanical stiffness between implant components and the host bone creates micromotion in the range of 150–220 µm, often sufficient to induce formation of fibro-cartilaginous tissues around the implant, but the extent of micromotion that is detrimental to clinical long-term stability is hard to evaluate. If the implant-host interface were totally unyielding throughout the surface of the implant, stresses and strains would probably lead to pathological periprosthetic bone fractures or implant fatigue failure. As this does not happen, it can be concluded that a well-fixed implant is at certain points tightly bound to host bone and tissues, but loose at some other points to allow micromotion. It could be stated that if parts of the implant are osseointegrated and stable, it is not possible that other parts of the same implant are more mobile. However, cancellous bone is deformable enough to evenly distribute strains. Therefore, assessing the actual nature of the bone-to-implant contact areas is an important research direction.

Total joint replacements are lubricated by synovial fluid-like fluid, namely hyaluronan, lubricin and

surface active phospholipid-rich pseudosynovial fluid. The joint works as a fluid pressure pump. Pressure at any point in a solution has that pressure transmitted equally throughout the solution (Pascal's law), so that when the joint volume is minimized, the pseudosynovial fluid may reach 700 mmHg pressures during walking. Oscillating fluid pressure probably causes dissection between implant and host tissues as pseudosynovial fluid penetrates between the implant and the surrounding fibrous capsule. The contact of the connective tissue with synovial fluid leads to the formation of a synovial-like lining on the tissue's surface. Pressure waves can cause pressure-induced tenderness and deep pain. Fluid movement in tubes is regulated by the Hagen-Poiseuille equation for a simplified Newtonian fluid:

$$\Delta P = (8\mu L / \pi r^4) Q \quad (1)$$

in which ΔP is the pressure change, μ is the fluid's viscosity, L and r are the tube's length and radius, respectively, and Q is flow rate. Small fluid shear stresses can stimulate osteocytes and osteoblasts. High fluid pressure can lead to osteocyte death, osteoclast recruitment and loss of bone support.

Technological developments have led to third-generation cementing techniques and better quality bone cement, forming an improved bone-to-cement interface for more uniform load transfer between the implant and host, and avoiding thrombo-embolic complications (1). Hydroxyapatite coatings have been developed as an alternative to cement fixation, and generally enhance osseointegration compared to porous coatings alone. On the other, use of NSAIDs for a short period postoperatively, with the rationale of preventing ectopic ossification, may increase aseptic loosening (2). This can at the present moment be best explained by its inhibitory effect on prostaglandin production, which is required for the initial bone repair. These interesting claims have been raised as a result of a recently published article entitled "Do non-steroidal anti-inflammatory drugs cause endoprosthesis loosening?" (3).

The effect of biomechanical load is illustrated by the fact that the longevity of many total joint replacements is better in elderly patients than in the younger patients despite the better bone stock in younger individuals. A less active way of life may have its virtues! Similarly, optimally placed implants lead to less peri-implant osteolysis and loosening as the stresses, strains and fluid pressure waves are more "anatomically" distributed, with less destructive strain or pressure peaks.

Microbial load

Sir John Charnley thought that loosening of a total hip replacement in the long term was due to indolent

infection (4). Foreign body reduces the minimal inoculum of *Staphylococcus aureus* that is required to cause an infection by a factor of more than 100,000. New microbes, including *Abiotrophia*, *Granulicatella* and "small colony" staphylococci, have been identified in the so-called aseptic loosening (5). Early postoperative implant infections are commonly caused by virulent microorganisms, such as *Staphylococcus aureus* and Gram-negative bacilli, whereas *S. epidermidis* and *Propionibacterium acnes* dominate delayed infections (6). Infections are increasingly rare and occur only in approximately 0.2% per implant year (7) with a mixed flora being involved in 10% of cases (5). Microorganisms that are associated with prosthetic joints typically grow in biofilms. On implant surfaces they organize into complex communities with structural and functional heterogeneity, resembling multicellular organisms. When dense enough they evolve the so-called "quorum sensing" based on intercellular signaling. Biofilm organisms show greater resistance to antimicrobial killing, probably secondary to reduction of the growth rate due to incomplete penetration of metabolic substrates (8). Since biofilm bacteria are also less susceptible to the immune system, implant-associated infections present a difficult challenge to orthopedic surgeons. Even the most potent combinations of antibiotics often fail to eradicate such implant-based infections, although temporary control and long-term prophylaxis are often possible. Ideal antibiotics should have bactericidal activity against surface-adhering, slow-growing and biofilm-producing bacteria (9). Rifampin perhaps fulfills best these criteria for Gram-positive bacteria, and quinolones for Gram-negative bacteria (10).

In North America two-stage exchange with 6 weeks of intravenous antibiotics is the preferred treatment, whereas debridement with device retention or one-stage exchange is performed less frequently than in Europe, where intravenous antibiotics typically are applied for a shorter period of time (11). Life-long suppressive antimicrobial therapy and permanent removal of implants are still indicated in particular cases.

Excluding indolent low-grade infection as a cause of implant loosening is difficult. Various methods, like multiplex polymerase chain reaction and reverse transcription of bacterial 16S rRNA sequences followed by sequencing of the transcripts will shed more light on this important question.

Even a dead enemy can be dangerous, as illustrated by the shift of the immunological paradigm from an ability to distinguish self from non-self, to an ability to distinguish dangerous from non-dangerous. Toll-like receptors (TLR) recognize microbially derived non-self, without the specificity of T-cell receptor or B-cell surface immunoglobulin, and can

contribute to the aseptic loosening by stimulating the local synthesis of e.g. tumor necrosis factor-alpha and interleukin-1 beta.

Particle load

The concept of "polyethylene disease" and then "particle disease" related to wear and material fatigue emerged concomitantly with the idea of aseptic loosening. Particle disease is considered to be caused by chronic foreign body inflammation (12). When the monocytes/macrophages phagocytose very small particles of implant-derived synthetic materials and attempt to destroy them, the result is recruitment of more cells, local activation of phagocytes and resident cells, release of pro-inflammatory cytokines and formation of foreign body giant cells, osteoclasts and granulomas.

If the phagocytes sense danger, they take up a fight they cannot win. The biological machinery, which can degrade and destroy all components of the extracellular matrix, including the tough collagen triple helix, is powerless in its fight against covalent and metallic bonds. Usually the host defense system simply puts more effort into the process, leading to foreign body inflammation with all of its consequences. One inadvertent consequence is local production of tumor necrosis factor-alpha, interleukin-1 beta (13) and, in particular, receptor activator of nuclear factor kappa B ligand (14). This series of events, together with locally produced macrophage-colony-stimulating factor, stimulate osteoclast formation and bone resorption (15,16), shifting the delicate osteoclast-osteoblast balance in a negative direction so that linear and/or polycyclic aggressive granulomatosis arises.

The strategy for avoiding particle disease has been to minimize particle production through development of hard-to-hard bearings (ceramic-to-ceramic, metal-to-ceramic, metal-to-metal), the use of non-wearable surface coatings, such as diamond coating, and the use of highly cross-linked ultra-high molecular weight polyethylene.

Innate host response against particles

After the best possible components are positioned according to the best current guidelines using proper fixation, eventual adverse host responses can still occur. Our understanding of bone biology has enabled great leaps forward in the management of systemic and local bone diseases. Vitamin 1,25(OH)₂-D₃ and calcium intake should be insured. Bisphosphonates can be used both locally and systemically to improve the early fixation of total knee replacements. This improved early fixation might lead to better longevity, but so far no data exist to indicate that bisphosphonates can halt an ongoing loosening process.

Bisphosphonates are chemically characterized by the P-C-P structure. This structure is required for binding of Ca²⁺ (e.g. bone hydroxyapatite) and binding of Ca²⁺ and Zn²⁺ ions (chelation). The geminal carbon of the bisphosphonate P-C-P contains R¹ and R² side chains. If R¹ is a hydroxyl group, the tridentate conformation formed enhances binding to calcium (hydroxyapatite). This is the reason for the "bone specificity" of bisphosphonates. R² determines their anti-resorptive potency. Based on the structure of R², two different chemical structures, structure-function relationships and modes of action are created. Non-nitrogen-containing "simple" bisphosphonates (e.g. clodronate and etidronate) do not contain any nitrogen in their R² side chain. They resemble pyrophosphate (PP_i) and are incorporated into non-hydrolyzable adenosine triphosphate (ATP) analogs via cytoplasmic aminoacyl tRNA synthetase. These ATP analogs cannot be hydrolyzed as they contain the non-hydrolyzable P-C-P backbone instead of the hydrolyzable (normal) P-O-P backbone. Non-hydrolyzable ATP analogs accumulate in the cytoplasm, interfere with cell metabolism and finally lead to osteoclast apoptosis.

Nitrogen-containing "complex" bisphosphonates (e.g. alendronate, ibandronate and risedronate) have bulky R² side chains. This prevents formation of ATP analogs as nitrogen-containing bisphosphonates are not metabolized. Instead, they are isoprenoid diphosphate lipid analogs and as such inhibit farnesyl diphosphate synthetase (FPP synthetase) of the mevalonate (cholesterol) pathway. The phosphonate group of these bisphosphonates fits into the diphosphate-binding site of the FPP synthetase enzyme, which is its major molecular target. Inhibition of FPP synthetase prevents formation of isoprenoid lipids and post-translational prenylation and geranylgeranylation of small signaling GTPases, such as Ras, Rho and Rac, which control many osteoclast functions. When these functions are disturbed, osteoclast apoptosis ensues. Locally delivered bisphosphonates in hydroxyapatite coating could slow down or prevent loosening (17,18).

Biotechnology enables the development of precision drugs that will target potent biomolecules as antagonists (blockers) or agonists (19). This approach is already apparent in the major changes that have occurred in managing difficult rheumatoid arthritis and Crohn's disease, based on the use of tumor necrosis factor-blockers or other biological agents (20). The greatest problem has become which targets to select for therapeutic intervention, in part due to legislation and regulations designed to "protect" the consumer that unfortunately also hamper optimal progress in drug development. Biologicals will hardly be specially designed to prevent or reverse loosening, but tumor necrosis

article

factor-blockers and teriparatide could find use as part of intelligent implants, which will release locally potent drugs inhibiting osteolysis or stimulating osteogenesis in peri-implant bone. Osteogenesis can also be stimulated with bone morphogenetic proteins and other similar molecules; for example, fibroblast growth factors are potent candidates for stimulation of periprosthetic osteogenesis.

Adaptive immune response against metal ions

Immunological responses can accelerate loosening. This response is usually caused by metal ions released as a result of corrosion, the gradual degradation of the metal due to electrochemical attack by the body's environment. All metals are subject to corrosion. Galvanic corrosion, for example, occurs when two different metals are in electrochemical contact. A similar phenomenon is seen in intergranular corrosion between impurities and inclusions at the grain boundaries and the bulk material inside the grains. Crevice corrosion begins at the bottom of small crevices containing fluid, e.g. between a screw and a plate. Electrolyte and pH changes, and local lack of oxygen (by impairing the formation of the passivating surface oxide layer) accelerate crevice and pitting corrosion. Fretting corrosion occurs at contact areas between materials under load subjected to vibration and slip, leading to micromotion and breakdown of the protective passive oxide layer. Stress (or tension) corrosion can occur in a metal subjected to stress, which creates electrochemical differences between the surfaces subjected to tensile and compressive stress. Corrosion resistance is of relevance for cementless, porous-coated implants and metal-to-metal gliding surfaces as they tend to lead to a potentially large corrosion surface area.

The adaptive immune system has the ability to differentiate self from non-self so that "horror autotoxicus" (autoimmunity in Paul Ehrlich's terms (21)) is avoided. Metallic ions can bind to self proteins as haptens, which may lead to their transformation to non-self recognized T-cell receptors. Lymphocytes can be found in relative abundance in cementless, metal-to-metal implants, and they may demonstrate oligoclonal T-cell receptor gene usage, indicating antigen-driven, oligoclonal T-cell activation. Such T-cells produce predominantly T-helper cell type 1 cytokines, including interferon-gamma, which sensitizes monocyte/macrophages and accelerates peri-implant bone loss.

Most cases of T-cell-mediated delayed-type IV hypersensitivity in total joint replacement patients probably do not occur because the patients become sensitized by the implantation of the components, but rather because they already possess this reaction pattern prior to surgery, perhaps as a result of prior

exposure to cheap jewelry through skin contact and body piercing. Potential total joint replacement candidates could be tested preoperatively using epicutaneous patch testing to assess induration and erythema, and *in vitro* stimulation tests to assess lymphocyte transformation and cytokine production in response to implant-derived ions, such as Cr^{3+} , Co^{2+} , Ni^{2+} and Ti^{4+} (22). The idea is to select implants that do not lead to hypersensitivity reactions. The problem with both epicutaneous and *in vitro* testing is that they do not reproduce the conditions of the peri-implant environment. Implant components may also contain many trace elements, which may be of significance due to the lack of dose-response coupling in immunological responses in contrast to toxic ones.

Conclusion

In well-performed "modern" knee and hip replacements, the success rate remains at 85–90% after 15–20 years of service. The skills of the operating and rehabilitation team probably also affect the outcome and the future quality of life of the operated patient. Improved control of disease activity, improved implant components and surgical technique decrease the need and improve the success for total joint replacements. Implant register studies have their drawbacks as, for example, the revision is used as the final outcome meaning that old and sick patients, who may have loosened joint implants, are "missed" from the statistics as they are not operated or refuse such an operation. Unlike drugs, which have to be validated with controlled clinical trials, such trials are not routinely performed with new implants. Nonetheless, with ten or more years without pain and with reasonable levels of function and quality of life, total joint replacement surgery is a success story in the modern musculoskeletal medicine.

Dedication



We dedicate this report to Seppo Santavirta, our late friend and Professor of Orthopaedics and Traumatology. Professor Santavirta made major observations on aseptic loosening, biocompatibility and diamond coatings and was continuously engaged in active international co-operation. His tireless dedication

both to research and to providing the best of clinical care inspired all of us who have contributed to this brief review. ■

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