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Leading opinion

The future of biologic coatings for orthopaedic implants

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ABSTRACT

Implants are widely used for orthopaedic applications such as fixing fractures, repairing non-unions, obtaining a joint arthrodesis, total joint arthroplasty, spinal reconstruction, and soft tissue anchorage. Previously, orthopaedic implants were designed simply as mechanical devices; the biological aspects of the implant were a byproduct of stable internal/external fixation of the device to the surrounding bone or soft tissue. More recently, biologic coatings have been incorporated into orthopaedic implants in order to modulate the surrounding biological environment. This opinion article reviews current and potential future use of biologic coatings for orthopaedic implants to facilitate osseointegration and mitigate possible adverse tissue responses including the foreign body reaction and implant infection. While many of these coatings are still in the preclinical testing stage, bioengineers, material scientists and surgeons continue to explore surface coatings as a means of improving clinical outcome of patients undergoing orthopaedic surgery.

1. Introduction

Orthopaedic implants are used routinely worldwide for fixation of long bone fractures and non-unions, for correction and stabilization of spinal fractures and deformities, for replacement of arthritic joints, and for other orthopaedic and maxillofacial applications. The primary aim of these devices is to provide mechanical stabilization so that optimal alignment and function of bone can be maintained during physiologic loading of bones and joints. In this way, the implants facilitate the relief of pain and more normal use of the injured limb or body part, and thus foster earlier return to function. By providing stability to bone fractures for example, orthopaedic implants indirectly assist in the biological aspects of bone healing by decreasing unwanted shear stress [1]. Similarly, devices that minimize micromotion at the bone-implant interface of cementless joint replacements, and unwanted movements between opposed bone surfaces in spinal fusion will enhance bone formation and remodelling [2–4]. The mechanical and biological aspects of bone healing are closely inter-related and ultimately determine final clinical outcome.

Historically, the design of orthopaedic fixation and reconstructive devices has focused primarily on the mechanical properties and function of the implant. In fracture fixation for example, this concept purports that bone will "heal by itself" if appropriately stabilized. However, this approach is shortsighted. Indeed in the USA, there are approximately 600,000 fractures with delayed union and 100,000 cases of nonunion each year [5]. Cementless joint replacements do not always osseointegrate with the surrounding bone, which may lead to implant migration and possible loosening [6]. Spinal fusion is not always a certainty [4].

The ultimate purpose of surgery employing a device is to help obtain, restore, or improve pre-morbid function. This goal may be compromised due to many potential factors including patient characteristics (e.g. chronic systemic metabolic disease, chemotherapy, smoking, excessive alcohol use, diabetes, medications, poor compliance with rehabilitation), local factors (e.g. difficult anatomical site and high degree of comminution of fractures, extensive injury to the soft tissue bed, infection, poor vascular supply, irradiation), and surgical and implant factors (suboptimal bone reduction, surgical technique, or application of the implant, inadequate implant characteristics) [5]. These facts have stimulated research into how the biological milieu of the implant bed could be modulated in order to help ensure a more robust bone healing response. The potential advantages are readily apparent: more vigorous, and expeditious bone healing would allow earlier rehabilitation and return of function. Although systemic pharmacological treatments to accomplish this goal have been considered, local strategies have

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several advantages including local targeted anatomic delivery of one or more biologics to the injury site, lower overall dosage requirements, and mitigation of potentially serious systemic side effects. This review will address strategies to improve bone healing (for example of fractures, non-unions, spinal fusion) and implant osseointegration for joint replacement via local delivery of molecules via implant coatings.

Orthopaedic devices may function in an appropriate fashion mechanically and biologically, however acute and chronic infection are potential dreaded complications that may necessitate further surgery. Infections of orthopaedic fracture and reconstructive devices occur in approximately 5% of cases and total about 100,000 cases per year in the USA alone [7,8]. For primary total hip replacement, the surgical site infection rate varies from about 0.2% to 2.2% [9]. Despite a comprehensive infection surveillance program, the rate of deep surgical site infection for primary hip replacement in the Kaiser Permanente registry in the USA was recently reported to be 0.51% [9]. Infections in spine surgery occur in approximately 2%–5% of cases [10]. Implant infections are a substantial cause of morbidity and even mortality, and are very costly to the patient and society in general [8].

Implant infections are not only a consequence of host factors (such as obesity and chronic medical conditions) and surgical technique [9]. The anatomical site and characteristics of the implanted device including size, shape, material, topography and intended use are important variables [7]. The use of prophylactic systemic antibiotics has been shown to dramatically reduce the incidence of implant related infections [11,12]. However, there are additional opportunities for local delivery of antibiotics and other anti-infective agents. Antibiotic containing bone cements appear to reduce the risk of infection in joint replacement surgery, although this point is controversial [12,13]. Thus there are ongoing opportunities to coat the implant directly with antibiotics or other biomolecules to reduce implant related infections [10,14].

This opinion paper reviews methods to coat prostheses implanted into bone in order to enhance osseointegration and mitigate adverse events associated with the foreign body response or infection. These implants of the future will hopefully modulate the local environment in a favourable manner with minimal risks, to improve patient outcome.

2. Coatings to enhance osseointegration

2.1. Calcium phosphate-like coatings

2.1.1. Mechanism of action and clinical results

Bone is a composite structure composed of cells, protein (mainly collagen and other signalling proteins) and mineral. The inorganic mineral phase of bone constitutes about 50% of its weight and is mainly composed of carbonated hydroxyapatite (HA). Coating the surface with HA has been shown to improve osseointegration of a cementless metallic prosthesis within bone [15,16]. HA is chemically similar to the apatite of the host's bone, and is a source of calcium and phosphate to the bone-HA interface [17]. Sintered HA can form tight bonds with living bone with little degradation of the HA layer. However, suboptimal fatigue properties of sintered HA have lead to the development of thinner coatings (about 30–100 μm) for application to a titanium implant substrate via plasma spraying. Other techniques of HA coating have also been introduced including sputtering, pulse layer deposition and electrostatic multilayer assemblies fabricated using the layer-by-layer technique [18]. The shear strength of HA plasma-sprayed titanium alloy implants in animal models is similar to the shear strength of cortical bone [17]. Osteoblasts form osteoid directly on the HA surface coating, suggesting that the bone-implant interface is bonded both chemically and biologically to the HA. Traditionally, HA coatings have been thought of as osteoconductive. However, calcium phosphate biomaterials with certain 3-dimensional geometries have been shown to bind endogenous bone morphogenetic proteins, and therefore some have designated these materials with osteoinductive properties [19].

HA coatings have been shown to enhance new bone formation on an implant surface with a line-to-line fit, and in situations where there are gaps of 1–2 mm between the coated implant and the surrounding bone. In canine studies, new bone formation was found even at distances of 400 μm from the HA surface, suggesting a gradient effect to the osteoconductive properties of HA [20]. Furthermore, the presence of an HA coating prevents the formation of fibrous tissue that would normally result due to micromovements of an uncoated titanium implant [21].

The bioresorption of HA coatings is still a matter of controversy. The two main methods of resorption include one that is solution mediated (dissolution), and another that is cell mediated via phagocytosis [22,23]. The HA coatings undergo variable resorption which is dictated by numerous chemical, biological and mechanical factors including the composition and physico-chemical properties of the coating, the anatomical location, and whether micromotion is present at the interface with bone [24]. Increased crystallinity appears to slow resorption of HA, and decrease bone ingrowth [25]. Mechanical instability hastens the dissolution of HA [20].

Hydroxyapatite coatings not only provide a mechanism to enhance osseointegration, but function to seal the interface from wear particles and macrophage associated periprosthetic osteolysis [26,27]. The majority of studies of total hip replacement have shown improved fixation with a decrease in the number of radiolucencies around an HA coated titanium alloy femoral component [28,29], although others have shown no differences between coated and uncoated implants [30,31]. A recent systematic review of randomized controlled trials of porous coated femoral components with or without HA in primary uncemented total hip replacement demonstrated no benefit [32]. However, there have been reports of adverse events associated with these coatings, which may fragment, migrate and even cause increased polyethylene wear secondary to third body abrasive wear [33–36]. Many of these adverse events have been found with first generation thicker HA coatings, and may be less relevant to current implants with thinner more uniform HA coatings.

Recently, HA coatings have been used not only for their osteoconductive properties, but as a method for delivery of growth factors, bioactive molecules, and DNA [18,37,38]. For example, HA coatings augmented with bone morphogenetic protein-7 (BMP-7) placed on segmental femoral diaphyseal replacement prostheses improved bone ingrowth in a canine extra-cortical bone-bridging model. Titanium alloy plasma-sprayed porous HA coatings infiltrated with collagen, recombinant human bone morphogenetic protein (rhBMP-2) and RGD peptide improved mesenchymal stem cell (MSC) adhesion, proliferation and differentiation in vitro, and increased bone formation in ectopic muscle and intra-osseous locations in vivo [18]. Another group used hydroxyapatite nanoparticles complexed with chitosan into nanoscale non-degradable electrostatic multilayers which were capped with a degradable poly(β-amino ester) based film incorporating physiological amounts of rhBMP-2 [39]. Plasmid DNA bound to calcium phosphate coatings deposited on poly-lactide-co-glycolide (PLG) were shown to be released in vitro according to the properties of the mineral and solution environment [37]. These methods of delivery of bioactive molecules extend the function of HA as a coating to enhance new bone formation on orthopaedic implants. The biologics added to HA must be introduced at the appropriate time (some are heat