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Review

Bone and metal: An orthopaedic perspective on osseointegration of metals

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ABSTRACT

The area of implant osseointegration is of major importance, given the predicted significant rise in the number of orthopaedic procedures and an increasingly ageing population. Osseointegration is a complex process involving a number of distinct mechanisms affected by the implant bulk properties and surface characteristics. Our understanding and ability to modify these mechanisms through alterations in implant design is continuously expanding. The following review considers the main aspects of material and surface alterations in metal implants, and the extent of their subsequent influence on osseointegration. Clinically, osseointegration results in asymptomatic stable durable fixation of orthopaedic implants. The complexity of achieving this outcome through incorporation and balance of contributory factors is highlighted through a clinical case report.

1. Introduction

The value of the global orthopaedic implant market, including joint replacements, spinal and trauma implants, was estimated at over US$30.5 billion in 2012 [1]. In 2012, the UK National Joint Registry recorded 86,488 primary total hip replacements (THRs) and 9,678 revisions [2]. The long-term implantable joint replacement hardware is broadly subdivided into cemented and uncemented, and of the primary THR operations, 43% were uncemented and 20% hybrid [2]. Uncemented implants rely on the process of osseointegration for their incorporation into the bone and long-term survival. The term "osseointegration", derived from the Latin words "os" (meaning bone) and "integrare" (meaning make whole), was initially coined by Professor Per-Ingvar Brånemark in the late 1950s, following the observation of bone and titanium integration [3], secondary to the formation of a direct interface between remodelled viable bone and the implant [4]. This interface is expected to be free of any evidence of the inflammatory response, and fibrous or connective tissue formation [5]. Osseointegration was clinically defined as "a process whereby clinically asymptomatic rigid fixation of alloplastic materials is achieved, and maintained, in bone during functional loading" [6]. In essence, implant osseointegration can be disrupted early, leading to the loss of primary stability and early migration, likely necessitating early revision [7], or late, resulting in the implant loosening. Currently, aseptic loosening is the most common cause of revision in hip and knee arthroplasty, accounting for 40% and 32% of all cases, respectively [2]. Specifically, early aseptic loosening is likely to be related to the issues of material and implant design affecting osseointegration. This emphasizes the need to optimize osseointegration in order to reduce and ultimately avoid revisions.

The extent and success of osseointegration depend on the biocompatibility of the implanted material. The concept of biocompatibility and its constitutive elements remain, to date, unclear [8]. Professor David Williams defined biocompatibility as "the ability of a material to perform with an appropriate host response in a specific situation" [9]. Over the last 25 years, the fields of orthopaedics and tissue engineering have progressed from the replacement and fixation of damaged mechanical elements to the application of regenerative medicine, including strategies to repair, replace and/or restore cells and tissues lost or damaged as a result of destructive mechanisms. The paradigm of generating an organized and functional tissue from expanded and appropriately stimulated stem cells with a matrix scaffold remains an attractive subject of intense research, although, to date, of limited commercial viability. Consequently, the design of orthopaedic implantable materials seeks to incorporate features capable of positively changing the dynamics of bio-integration (enhancing and improving the quality of host bone apposition to the implants). Biocompatibility was subsequently redefined as "the ability of a biomaterial to perform its desired function with respect to a medical therapy, without

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eliciting any undesirable local or systemic effects in the recipient or beneficiary of that therapy, but generating the most appropriate beneficial cellular or tissue response in that specific situation, and optimising the clinically relevant performance of that therapy" [8]. In essence, an implant needs to be sufficiently inert to avoid an undesirable systemic response (immune/inflammatory adverse reactions) and retain the capacity ideally to stimulate osseointegration.

Following implantation and attainment of primary stability through mechanical press-fit, the initial interface of an endosseous orthopaedic implant will still retain spaces and deficiencies that require native bone infill through the process of osteogenesis in order to achieve secondary stability. Post-implantation local bone resorption due to pressure necrosis further compromises primary stability. Secondary stability is achieved through the process of osteogenesis, which occurs either by lamellar remodelling or by woven bone deposition [10] on the surface of the host bone bed and on the implant itself, known as distance and contact osteogenesis, respectively [11]. Contact osteogenesis is responsible for colonization of an implant surface by osteogenic cells followed by the synthesis of extracellular bone matrix and subsequent appositional de novo bone formation [10], and is likely to be affected by the material used in implant fabrication.

The exquisitely orchestrated spatio-temporal events that occur during osteoblast development and bone formation are relevant to the deposition of osteoid at the bone–implant interface [12]. Thus, active proliferation takes place during the first 10–12 days after implantation, leading to the formation of cell focal nodules or multilayers. Subsequently, expression of extracellular matrix (ECM) protein genes including type I collagen, fibronectin and genes associated with the osteoblast lineage such as alkaline phosphatase are significantly elevated. During the post-proliferative phase (12–18 days), the ECM matrix matures and mineralization then occurs (osteopontin, osteocalcin and bone sialoprotein observed). Extensive mineralization at day 21 is associated with a reduction in alkaline phosphatase (ALP) activity and, at around day 28, osteocalcin and osteopontin activity falls. Hence, by 28 days most of the processes related to the osteoblast proliferation, differentiation and mineralization are thought to be complete. Interestingly, this aligns with clinical practice of 4–6 weeks protected weight bearing upon implant placement [12]. Any surface alterations should thus aim to enhance and accelerate the above time frames, as well as enhancing the strength of the implant–bone interface.

This review will focus on the mechanisms present at the bone–implant interface, the interaction of the surface of the orthopaedic device, specifically, the metal components and the modulation of contact osteogenesis and osseointegration. The material characteristics central to osseointegration and osteogenesis and thus implant biocompatibility include:

(i). material properties – specifically, bulk properties (Section 2.1) and surface properties (Section 2.2);
(ii). chemical (Section 2.2.1.1) and biochemical characteristics (Section 2.2.1.2);
(iii). corrosion characteristics and wear debris release (Section 2.2.2);
(iv). surface energy and wetting (Section 2.2.3);
(v). surface topography (Section 2.2.4).

2. Material properties

2.1. Bulk properties

The elemental makeup and structure of a material define its bulk properties [13], such as the elastic modulus, hardness, fracture toughness and wear resistance, which in turn are central to the performance of an implant. Currently, the majority of implants used in orthopaedic trauma and arthroplasty are metal in composition, due to their excellent mechanical strength [14]. The implants are developed from tailored metallurgical processing methods that define the bulk properties central to the implant–host bone interaction, biocompatibility and osseointegration.

The most widely used metallic biomaterials are titanium (Ti) and related alloys, cobalt (Co)–chromium (Cr) alloys and stainless steel [8,15,16]. Ti and related alloys, as well as Co–Cr alloys, display the greatest biocompatibility [8], aided by further alloying them with different elements and subjecting the materials to different processing routes to optimize toughness, ductility, tensile strength, fatigue strength and surface hardness. Ti alloys have therefore found widespread use as the gold standard in the parts of uncemented orthopaedic implants involved in osseointegration.

However, stiffness remains a significant limitation of metals. Wolff's law of bone remodelling states that mechanical load (i.e. strain) determines bone strength by affecting the bone architecture [17], and is an essential stimulus in the natural process of fracture healing and remodelling [18,19]. The femoral modulus of elasticity is known to deteriorate by ~2% each decade [20]. Thus, a significant mismatch between the elastic modulus of a load-bearing implant and that of the bone deleteriously affects the load transfer from the implant to the bone and within the bone, potentially leading to peri-implant bone resorption and implant loosening or bone fracture [15,16,21]. This is a phenomenon known as stress shielding. It has been noted in vitro and in vivo that osteogenic potential is enhanced by high strains, alternating periods of strain loading with rest, and high strain rates [22–24], with strain duration of 6 h suggested to be more effective than short load intervals in the induction of bone morphogenetic protein 2 (BMP-2), runt-related transcription factor 2 (Runx2) and osteocalcin gene expression in adipose-derived stem cells, thus modulating osteogenesis [25]. Furthermore, changing strain induces extracellular fluid flow, resulting in osteocyte cell membrane shear stresses [26] or generating streaming electric potentials [27]. Both mechanisms were noted to enhance the recruitment and function of osteoblasts in vitro [28,29]. Thus, stress shielding may result in peri-implant strain protection, inhibiting these complex cellular mechanotransduction mechanisms.

Ti alloys possess the most favourable specific strength (strength to density ratio) and lowest modulus of elasticity [15,30] in the group of metallic biomaterials, limiting the effect of stress shielding. The mechanical strength of pure Ti can be enhanced through modifying the microstructure of the material [31]. For example, the addition of Al and V stabilizes the α- and β-phases, respectively, creating a dual phase mechanically enhanced microstructure, which permits Ti–6Al–4V use in structural biomedical applications [15,31]. To address the Young's modulus being higher than that of cortical bone and issues of Al and V release, a new range of low modulus β-type Ti alloys was subsequently developed, incorporating a range of alloy constituents (e.g. Zr, Fe, Ta) [16]. Nb, Zr, Mo and Ta have proved ideal for lowering the elastic modulus while enhancing material strength [32,16]. Ti alloys exhibit excellent corrosion resistance due to surface oxide film formation [8,15]. However, the limitations of Ti alloys include poor shear strength, low wear resistance and high notch sensitivity [16,33,34], making them unsuitable for bearing surfaces.

The strength of pure Ti and its alloys can be enhanced by modifying the microstructure through grain refinement. Indeed, nanograined β-Ti alloys in vitro are able to elicit greater attachment and proliferation of fibroblasts [35], pre-osteoblastic cells [36] and stem cells [37]. This is likely a consequence of an alteration in the surface topographical characteristics resulting from increased nano-roughness, emphasizing the close interrelation between the bulk and surface properties of the materials.

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In addition to a high elastic modulus, stainless steel displays relatively poor wear and corrosion resistance [15,34,38]. Thus, despite its low cost, the poor wear and corrosion performance and the issues around Ni release (discussed later) limit the use of stainless steel to traumatology and osteosynthesis, where the in vivo presence of the implants is typically temporary, or use as long-term low-cost cemented implants [34]. Co–Cr alloys display excellent wear and corrosion resistance as well as significant fatigue strength as a consequence of their hardness, making these materials ideal for bearing surfaces [15,34].

2.2. Surface properties

The implantation of an orthopaedic device results in exposure of the surface to biological fluids and surface modification as a consequence of host ions and cells, leading to further tissue response/integration [39,40]. The process of surface colonization with recruited cells is relatively non-specific, and thus the ability to enhance host mesenchymal stem and progenitor cells is central to the differentiation of the stem/progenitor pool into mature osteoblasts secreting osteoid [10,41]. Chemical composition, surface energy, surface roughness and surface topography have all been suggested as vital factors affecting skeletal cell behaviour [40].

2.2.1. Chemical and biochemical properties

The cell–material interaction is determined by the material's surface characteristics [42], typically defined as the outermost 100 nm thick layer of an implant [43]. The surface chemical composition is representative of that of the bulk material although the surface will comprise highly reactive unsaturated bonds [44]. Whilst Ti and Co–Cr alloys demonstrate good biocompatibility, enhanced osteoblast adhesion was observed on Ti_6Al_4V surfaces in vitro [45]. Compared to Co–Cr, Ti alloys exhibit the ability for more rapid integration, generating a significantly stronger interface at 12 weeks in vivo [46]. Interestingly, Co–Cr alloys show a propensity for cartilage and unmineralized osteoid formation at the interface. Thus the ability to stimulate bone formation at the interface appears key to the attainment of implant primary stability.

Oxidation of Ti surfaces (which can occur at atmospheric conditions) and formation of a surface TiO_2 layer through the process of passivation is essential for improved osseointegration and a dynamic interface [43,47]. Typically, TiO_2 matches the topography and roughness of the underlying substrate, is ~2 nm thick and its chemical properties are related to the surface preparation [44], with a thicker TiO_2 layer enhancing surface wettability and osteoblast ALP expression [48]. Spontaneous nucleation of apatite crystals can occur on the surface of TiO_2 [49], induced by OH^- groups in the oxide layer on exposure to biological fluids [50]. Ellingsen has also shown that exposing TiO_2 to calcium in vitro resulted in calcium adsorption into the negatively charged oxide layer up to a depth of 17 nm, resulting in selective protein binding [51], although serum protein adsorption may have an inhibitory effect on the capacity of TiO_2 to induce nucleation.

2.2.1.1. Chemical modifications of metal surfaces. Ti and CoCr alloys are biocompatible, but not bioactive [8,31]. One of the methods of enhancing the anchorage of implants to bone is to induce bioactivity of the constitutive material by manipulating the chemical composition of the material [34,43]. Impregnation refers to integrating a chemical or biochemical adjuvant within the bulk of a material, e.g. alloys, where a true alteration of chemical composition is achieved [52]. Coating refers to the superficial deposition and bonding of a new chemical or biochemical adjuvant on the core material [53], while the process of rendering the material more bioactive is known as biofunctionalization [31].

Surface coating with inorganic molecules, e.g. calcium phosphate, increases osteoconduction in vivo [54]. Plasma spray coating with hydroxyapatite (HA) ($Ca_{10}(PO_4)_6(OH)_2$), remains one of the most common methods of surface modification of clinical implants [34,55] due to the similarity of HA to the mineral phase of the bone matrix [56], resulting in the induction of human mesenchymal stem cell differentiation in vitro [52]. HA coating doubles the strength of mechanical fixation compared to uncoated Ti implants at 4 weeks in vivo [57]. Calcium phosphate coating is thought to result in bioactive implants interacting with bone [55,56] through protein adsorption [10], while surface impregnation with Mg, S, P and Ca has been reported to drive osseointegration and improve bone-to-metal contact in vivo [58,59]. Strontium incorporation into the TiO_2 layer resulted in enhanced cell attachment, spreading and osteoblast differentiation in vitro [60]. Surface modification with fluoride resulted in an increase in the number of attached cells in vitro [61], induction of osteoblast differentiation, higher mineral density at the interface and improved pull-out force in vivo [62,63], possibly by altering the surface chemistry and nanotopography [52,54].

A reverse approach to stimulating osteoinduction has been to inhibit bone resorption through targeted site-specific delivery of bisphosphonates on implant surfaces. Bisphosphonate-modified Ti implants were shown to result in significantly enhanced early new bone formation at the interface in vivo [64], likely, as a result of inhibition of peri-implant bone resorption [65] even in the presence of particulate wear debris [66]. Prieto-Alhambra et al. have shown a significant implant survival increase in patients undergoing clinical oral bisphosphonate therapy [65]. However, resorption is a key component of the bone remodelling process, and there are reports of "atypical" femoral, including periprosthetic, fractures related to long-term bisphosphonate use [67].

2.2.1.2. Biochemical modifications of metal surfaces. The surface chemical composition is important for protein adsorption and subsequent cell adhesion [10,60] through transmembrane cell receptors (integrins) [34], interacting via specific ECM amino acid sequences, in particular Arg-Gly-Asp (RGD) [55,68]. Biofunctionalization of the surfaces with organic molecules has thus received significant interest under the wider umbrella of biochemical modification of titanium surfaces (BMTiS) [69]. These modifications include linking of peptides, bone morphogenic proteins and growth factors, ECM proteins and pharmacologically active molecules. BMP is known to induce osteogenic differentiation [70], and BMP/vascular endothelial growth factor (VEGF)-coated Ti implants were demonstrated to enhance bone mineralization in vivo [71]. Collagen and collagen + BMP coated implants demonstrated superior osseointegration in vivo, although there was no significant difference between the coated groups [72]. In contrast, the volume of in vivo bone deposition was reduced on BMP-2 functionalized implant surfaces [73], possibly due to BMP-induced osteoclast differentiation and activation [74]. In other studies, supplementation of morselized bone allograft with BMP-2 increased the rate of allograft resorption, reducing implant stability [57]. Although the systemic half-life of BMP was shown to be less than 20 min, this could be prolonged when delivered in association with collagen [75] and heparin [76]. However, reports of host immune responses against recombinant BMP [75] call into question the clinical biocompatibility issue of BMP-2 peptide surface modifications.

Xiao et al. described one of the earliest attempts to link RGD-sequence-containing peptides to titanium surfaces [77], and subsequently it was shown that RGD-modified Ti surfaces could promote osteoblast attachment, compared to unmodified surfaces in vitro [78]. It was suggested that increasing the concentration of linked peptide sequences significantly improved osteogenic

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mineralization [79]. Zreiqat et al. demonstrated that RGD-peptide-modified Ti alloy surfaces enhanced osteoblast differentiation and osteoid production, as well as osteoclast differentiation and thus, potentially, bone remodelling in vitro [80]. In vivo studies have also shown a likely beneficial effect of Ti surface RGD modification on bone formation and ingrowth, reduction in fibrous tissue formation, and improved implant fixation [81,82].

Collagen exerts considerable influence on osteoblast behaviour in vitro, enhancing differentiation and adhesion [83]; thus, collagen coating of Ti and Co–Cr alloys appears attractive, although in vitro experimental results are contradictory [84,85], whilst in vivo studies indicate that there is no advantage on peri-implant bone formation in pre-coating Ti surfaces with collagen over RGD-containing peptides [72]. The enhancement of peri-implant bone formation has been shown to be similar in collagen pre-coated surfaces and acid-etched rough Ti surfaces [86]. In order to prevent implant colonization and formation of a biofilm, immobilization of antibiotics onto titanium surfaces was shown to be successful in resisting infections in vitro [87].

2.2.2. Corrosion characteristics and wear debris release

Metals exposed to corrosive biological fluids inevitably undergo corrosion to some degree [88–90]. The breakdown of the protective surface oxide layer subsequently results in exposure of the nascent surface to corrosive attack and the potential release of metal ions from an anode [90]. Four types of corrosion have been observed in orthopaedic practice: (i) galvanic corrosion occurs when there is an electrochemical potential difference between two different metals, or between different areas of the same metal surface, when immersed in a biological fluid; (ii) pitting corrosion is caused by the localized depassivation of the surface, or localized areas of different potential due to the material microstructure, with autocatalytic metal dissolution within the formed pits; (iii) crevice corrosion is similar to pitting corrosion and occurs in confined spaces, where low oxygen tension, low pH and high chloride concentration lead to destruction of the passivation layer; and (iv) in fretting corrosion, the passivation layer is mechanically broken down due to micromotion between parts of an implant, exposing the nascent surface to corrosive attack [91]. While crevice corrosion is more likely to occur at the attachment site of metal parts, pitting and fretting corrosion, as well as wear, affect the bearing surfaces.

The process of corrosion is dependent on the bulk and surface material properties, as the elements of the bulk of the material are released from the surface. This process is different from the wear discussed below, which results in the production of particulate debris, although the processes of corrosion and wear are closely linked [92]. Experimental fretting wear accelerates the rate of corrosion [93], including metal ions released not only as a consequence of depassivation of the contacting surfaces, but also from corrosion of the wear particles resulting in an increase in the metal surface area in contact with corrosive body fluids [93,94]. Clinically, these ions are found locally and systemically [95]. Recently, a degree of metal ion release has been attributed to corrosion at the head-neck taper [96,97], indicating a combination of mechanical fretting and crevice corrosion [96,98,99]. However, as metal ions are known to be released from other devices not subjected to mechanical friction (e.g. endovascular stents) [89], the electrochemical process of corrosion appears evident. Certain transition metals, including V, Cr, Co and Ni, are known to cause systemic effects of neurotoxicity, hepatotoxicity and nephrotoxicity [100]. In addition, V release can lead to haemolysis, anaemia, decreased fertility, embryotoxicity and teratogenicity [101]. Al neurotoxicity has been suggested to be secondary to the impairment of mitochondrial biogenetics [102]. Released metal ions can also activate the immune system, either directly or by acting as haptens and forming complexes with native proteins [103,104]. Thus, a significant number of patients with orthopaedic implants developed increased sensitivity to the alloy constituents [88,104]. Allergic contact dermatitis is commonly triggered by Ni, Co and Cr [105,106], and indeed sensitization to Ni by consumer products and subsequent contact dermatitis resulted in the 1994 EU "Nickel Directive" regulating consumer Ni exposure; although this remains an issue [106]. In the UK, the prevalence of Cr and Co dermatitis in patients was reported to be as high as 6% and 4%, respectively [107]. The increased rate of haematopoietic malignancies reported following metal-on-metal (MoM) joint replacements may be as a consequence of metal particles activating the pre-malignant lymphoid tissue associated with osteoarthritic inflammatory changes [108].

Critically, metal ions have been shown to exert a direct cytotoxic effect on peri-implant cells [92]. Ni, Al, Fe and, especially, Co and V, were demonstrated to be toxic, reducing proliferation and viability, and inducing alterations in cell morphology of peri-implant cells at concentrations found in vivo in patients with joint arthroplasties [92]. V cytotoxicity and mitogenicity were also shown to lead to morphological neoplastic transformation in vitro [109]. A significant reduction of mouse fibroblast and osteoblast growth rates was found in the presence of V and Al in vitro, with the combination being almost synergistic at producing cytotoxicity [110]. The authors also demonstrated the wear particles from Ti–6Al–4V alloys exhibited a similar cytotoxic effect in vitro. Al preconditioning of osteoblasts in vitro has been shown to affect osteocalcin production in a dose-dependent manner [111]. At sub-lethal doses of V elicited gross delayed cytotoxicity, Ti and Al produced suppression of osteocalcin deposition and matrix mineralization, while Co–Cr–Mo alloy had little effect [112]. Soluble Ti and V encouraged superoxide anions release by the neutrophils in vitro [113] and metal ions have been implicated in enhanced macrophage resorptive function, osteoclast differentiation and osteoclast-mediated surface corrosion [114–116]. Subsequent metal ion release could potentially trigger osteolysis, altering the bone remodelling equilibrium and ultimately precipitating bone loss and prosthetic loosening [88].

Bearing surfaces can influence the bone–implant interface through the wear particles released. Co–Cr alloys wear particles were linked to cytotoxicity, non-specific inflammatory reactions, adverse macrophage responses, lymphocyte-dominated immunological hypersensitivity reactions (i.e. aseptic lymphocyte-dominated vasculitis-associated lesions – ALVAL), and pseudo tumour formation [108,114,117–121]. The type of adverse reaction and the amount of induced cytotoxicity most likely depend on a combination of the nature of a material subjected to wear and individual patient factors modulating the responses. Locally generated cytokines trigger an intense recruitment and differentiation of osteoclast precursors [88,122]. These harmful reactions disrupt the stable bone–implant interface, eventually resulting in osteolysis and aseptic loosening, compromising implant functioning and survivorship. This remains a significant orthopaedic issue, and currently aseptic loosening accounts for 40% and 32% of all total hip and knee joint replacements, respectively [2], although the mechanism of the majority of these cases is commonly attributed to polyethylene wear. However, clinical revision rate of MoM hip replacements was observed to be 6.1% in females at 5 years [123].

Thus, whilst many of the metal materials that are considered biocompatible are usually well tolerated, these materials are not inert, and consequently, Ni-free stainless steels and Co–Cr alloys, and V- and Al-free Ti alloys, are in development in an attempt to balance biological incompatibility together with the practical need for metals [31,34]. This balance is currently superior in Ti and Co–Cr alloys [8].

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2.2.3. Surface energy and wettability

The surface energy is an excess free energy per unit area created when a surface is established. The surface energy of a material can be calculated from its wettability with water and subsequent measurement of contact angles made by the water drops [124], with high contact angles indicating hydrophobicity, and low angles indicating hydrophilicity. This energy increases with increasing roughness in transition metals, i.e. Ti [124], and is of importance as material surface energy impacts on cell function.

The propensity and strength of in vitro cellular adhesion to metal surfaces appears to be directly proportional to the surface energy and hydrophilicity [125,126]. Hydrophilic rough Ti surfaces were able to induce more osteoblast differentiation and release of local growth factors in vitro, although cell proliferation was impaired [127]. Controlling surface roughness while increasing the wettability in vitro resulted in reduced cell numbers and enhanced osteoblast differentiation [128], whilst in vivo experiments demonstrated that increased wettability of implant surfaces resulted in better initial bone apposition and bone–implant contact [129]. Hydrophilic surfaces aid cell adhesion through adsorption of matrix proteins such as fibronectin and collagen [43,124]. Surface hydrophilicity and protein adsorption decrease with extended storage time – a phenomenon known as titanium-specific biological ageing [130], which is believed to be linked to increasing hydrocarbon surface contamination [126]. Alternatively, increased bioactivity of the hydrophilic TiO_2 layer could be related to the surface basic and acidic hydroxyl groups [49], which appear to modify the strength of cell surface integrin binding to fibronectin-coated surfaces in vitro [131]. Hydrophilic surfaces are able to adsorb the proteins in a more flexible conformation in vitro, permitting their reorganization by the adhering cells [125], and improved adhesion and spread of cells [132]. Conversely, Roach et al. found that in vitro fibrinogen-binding affinity is stronger on hydrophobic surfaces [39], and that the secondary structure of the proteins adsorbed onto hydrophobic surfaces was less organized [39]. Furthermore, lower surface energies were shown to achieve greater fibronectin adsorption and greater fibronectin-mediated cell proliferation in vitro [133]. These inconsistencies may be explained by either the variation within experimental methods, or by the fact that exceptionally high surface wettability is inhibitory to stable protein adsorption, cell adhesion and proliferation [124].

Chemical modifications can alter surface wettability and roughness [60,124]. Thus, surface energy, chemical composition and topography of Ti surfaces all exert complex physicochemical influences on cell function, integrin expression and VEGF production in vitro [134]; a view further supported by the work of Aita et al. [126] and Lamolle et al. [61]. Sommerfeld et al. indicated that the relationship between nano-structure, surface energy and protein adsorption was not linear [135]. Exposure to UV light rendered hydrophobic surfaces superhydrophilic (photofunctionalization). This conversion to wettability was reversed by storage of materials in the dark or exposure to the atmosphere [136]. UV photofunctionalization of Ti surfaces enhances protein adsorption, osteoblast attachment, proliferation and phenotype expression in vitro, and implant fixation in vivo [126]. Hence, UV treated surfaces stimulated simultaneous osteoblast proliferation and differentiation, thus accelerating bone formation without compromising bone mass. These findings highlight the controversies in understanding the potential role of surface energy in osseointegration. Clinically, storage, sterilization methods and exposure of implants to air prior to implantation are thus important considerations. However, implant UV treatment pre-implantation to enhance osseointegration [126] and to overcome the phenomenon of biological ageing [137] is appealing. Indeed, this strategy has been tested clinically, with enhanced achievement of stability in photofunctionalized implants leading to faster loading protocols of oral implants [138].

2.2.4. Surface topography

The phenomenon of shaping cell morphology by the physical environment is known as surface guidance [139]. Osteoblast adhesion to implant surface, proliferation and differentiation are significantly influenced by surface topography [44]. The topographical modifications can be introduced with additive (i.e. coatings) and subtractive methods (i.e. etching), which lead to overall enlargement of the surface area [42,140], while potentially altering surface chemical composition and energy [42,43,140]. The advantages of topographical stimulation of lineage-specific differentiation are its stability and durability, relative ease of manufacture and avoidance of highly regulated bioactive substances [41,141]. Moreover, the advantage of nanotopography is the high surface-to-volume ratio afforded by nanotopography [142]. Surface topography is defined by surface orientation and roughness [140], and is characterized by a succession of peaks and valleys [43]. To date, no substantial evidence has been presented on surface orientation affecting implant osseointegration, once the effect of roughness is controlled [140]. In contrast, surface roughness is crucial for bioengineering and is dependent on [143,124]: (i) macro-roughness, (ii) micro-roughness, (iii) ultra-roughness, (iv) submicron roughness and (v) nano-roughness.

Distinct roughness levels result in discrete effects on living tissues [143]. On a three-dimensional (3-D) areal scale, rough surfaces were defined as the average height deviation (S_a) of >2 μm, moderately rough surfaces S_a of 1–2 μm, minimally rough surfaces S_a of 0.5–1 μm and smooth surfaces S_a < 0.5 μm [144].

Moderate surface roughness has been associated with stronger bone responses in vitro and in vivo [43,145], and a potential optimal range of roughness for implant osseointegration [42]. Ronold et al. demonstrated an increase in the interface tensile strength with increasing roughness up to S_a of 3.9, beyond which the correlation reversed [42]. This effect is not related to the increased metal ion release from the surface-enlarged implants [145]. On a cellular level, moderate roughness may be more optimal for cell attachment, with excessively rough surfaces leaving unduly long distances between their peaks that cells perceive them as flat, and flat surfaces causing excessive cells flattening and compromising their nutrition [140]. The changes in the adhesion spread of the cells lead to morphological transformations, and will be discussed later [41,146]. On a mechanical level, exceptionally rough surfaces only achieve contact at the peaks, while flat surfaces do not offer sufficient frictional resistance to displacement. Critically, in vivo bone requires spaces of at least 50 μm for successful turnover and remodelling [147], resulting in the area of functional osseointegration being smaller than the theoretical surface area on the surfaces with tightly spaced peaks.

The effect of macro-roughness is largely mechanical, with the irregularities mechanically strengthening the implant anchorage, but being too large to be recognized by cells [124]. In contrast, micro- and ultra-topographies appear to influence osteogenesis through alterations in mesenchymal stem cell behaviour [143].

Existing machining processes, surface characterization techniques and measuring equipment give rise to quite a wide range of reported surface roughness characteristics [41,140]. The data presented often measure roughness as either S_a or R_a (graphically explained in Fig. 1), making comparisons of height parameters difficult. Equally, a spatial or hybrid parameter needs to supplement a height parameter for an adequate understanding of surface topography [43,140,144]. As a consequence, controversial outcomes are reported for micro-rough surfaces. Moderately rough Ti surfaces (S_a = 1.2 μm, roughness being well defined with additional parameters) in vitro influenced osteoblast morphology, inhibited cell proliferation, and enhanced ALP activity, osteocalcin expression (in synergy with $1\alpha,25(OH)_2D_3$) and local production of TGF-β_1 and prostaglandin E2 (PGE_2), when compared to smoother surfaces

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with S_a = 0.6 μm [127], with a degree of this effect being attributed to the surface energy. Generation of TGF-β_1 and PGE_2 molecules further enhances the osteogenic microenvironment. Similarly, cell proliferation was inhibited and cell differentiation promoted by the rough surfaces with R_a > 4 μm in vitro [148]. In this study, despite enhancement in osteocalcin, TGF-β_1 and PGE_2 secretion, ALP expression was reduced by the rough surfaces in cells of all maturity levels. Rough Ti–6Al–4V surfaces with R_a > 2.5 μm reduced proliferation, induced osteogenic differentiation and increased expression of β-actin and ERK2 genes in vitro [149]. β-actin is involved in cytoplasmic streaming during locomotion or cell shape alterations, while ERK2 (p42 mitogen-activated protein kinase – MAPK) regulates proliferation and differentiation. Actin cytoskeleton interacts with MAPK [150], which will be discussed in more detail later. The in vitro effect of rough microsurfaces and $1\alpha,25(OH)_2D_3$ on osteoblast differentiation was found to be synergistic and dose-dependent [148,151,152]. Therefore, the general tendency is for the rougher surfaces to suppress proliferation, while stimulating differentiation. On the other hand, Ti alloy surfaces with R_a = 0.87 μm were found to promote cell attachment and proliferation more effectively than R_a = 0.32 μm, possibly as a result of a 10-fold increase of fibronectin adsorption on the rougher surfaces in vitro [153]. Anselme found that cells exhibited reduced proliferation and differentiation on rougher (R_a > 2 μm) and less organized surfaces, with the highest cell numbers observed on the surface with R_a = 0.16 μm [44]. These disagreements may be due to incomplete surface characterization, or the fact that the osteogenic response is dependent on the maturation state of the cells [148]. Lohmann et al. found that osteogenic differentiation stimulated by the rough surfaces is more pronounced in less mature cells [148]. In vivo studies reveal higher interface strength achieved by rougher surfaces [154]. Wennerberg and Albrektsson concluded that on the basis of evidence from in vivo and clinical studies, there is an indication that microtopography enhances bone responses, leading to stronger osseointegration [140].

Nanotopography is possessed by all material surfaces, and is subtly different to nanostructure, which incorporates nanotexture and nanopattern [43]. Nanotopographic surface modifications hold great promise [124,140,141]. Bone features possess an array of magnitudes [19]. Mineral crystals and collagen fibres are measured in micro- to nanometers, and naturally do not exhibit a high level of organization [41]. Mineralized osteoid contains an intricate blend of fibres, pits and protrusions [155]. Therefore, nanotopographies can be designed to mimic these nanofeatures, stimulating an appropriate response. The nanotopography manufacturing process allows for enhanced control over the surface [41], in turn, permitting the study of the effect of texture and its organization. The effect of nanotopography, to date, appears to be unaffected by the surface material [156], and was shown to contribute to osteogenic differentiation by upregulating the transcription factor Runx2 phosphorylation [157]. Human mesenchymal stem cells (hMSCs) cultured on 15 nm nanotopographical cues were most optimally spread and cytoskeletally organized, and expressed the highest levels of osteocalcin and osteopontin, compared to 55 and 100 nm cues [156]. The same group indicated that nanostructuring of surfaces with islands of 33 nm elicited more specific integrin and ERK gene up-regulation than 362 nm deep pits or exposure to dexamethasone [158]. Genetic modulation by nanocues appears more selective than by dexamethasone. Activation of pathways related to adhesion and cytoskeleton agrees with a mechanism involved in focal adhesion assembly and signal transduction [150]. Rho regulates this process by triggering the aggregation of integrins at focal adhesions [159], which initiate signal transduction of the stimuli from the ECM to the nucleus via dynamic intracellular protein interactions, resulting in nuclear deformation and modulation of genetic activity [160]. Rho GTPase activation in combination with cytoskeletal tension induced by actin fibres was found essential for in vitro commitment of MSCs to osteogenic lineage [146]. In vitro and in vivo investigation of Ti surfaces with 20, 30 and 50 nm nanopores showed upregulation of Runx2 transcription factor, ALP and osteocalcin expression, and the highest bone–implant contact and pull-out strength on the largest nanopores [161]. Zhang et al. revealed that, compared to 10 nm wide cues and planar controls, nanodimensional cues of 30 nm triggered amplified cell adhesion and expression of Runx2, ALP, osteopontin and osteocalcin genes in vitro [162]. The surfaces with larger nanocues were also shown to be more hydrophilic [162]. Oh et al. observed that TiO_2 nanotube diameters of 70 and 100 nm, and not 30 nm, caused significant cell elongation, filopodia formation and increased cytoskeletal stress, resulting in preferential osteogenic differentiation in vitro [142].

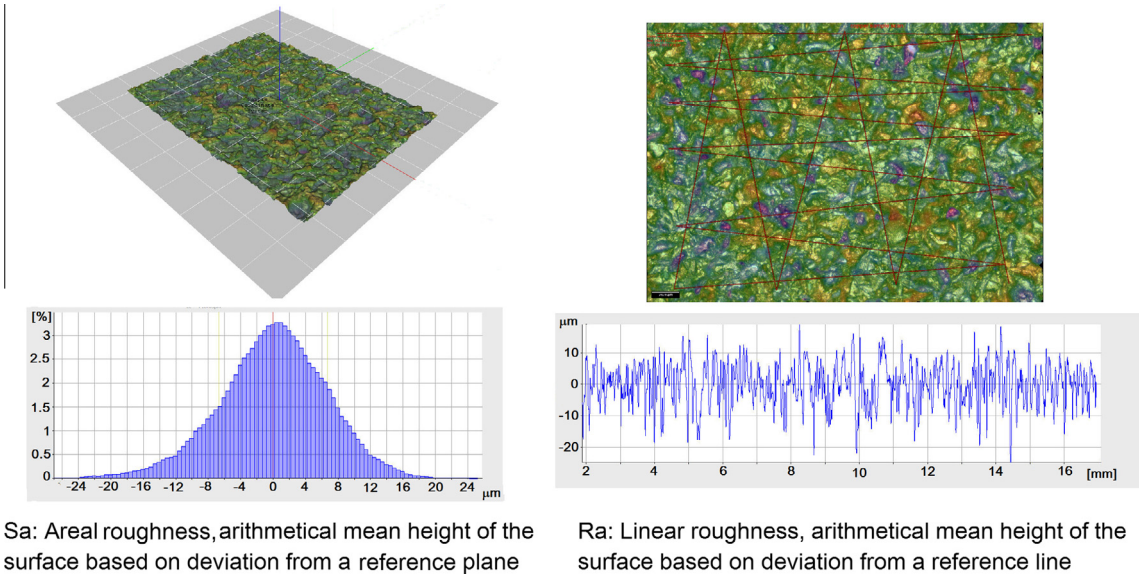

Fig. 1. Graphical comparison of S_a and R_a measurements of the surface roughness.

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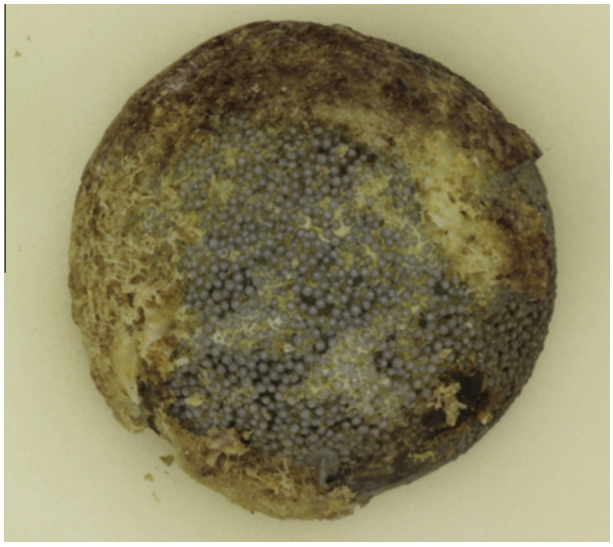

Fig. 2. Retrieved Co–Cr acetabular cup porous surface of cast beads demonstrates successful bone on- and in-growth.

The effect of specific nanotexture dimension on osteogenic stimulation of hMSC is potentially related to the formation of cell adhesions and the resultant alteration of intracellular tension [41,160]. Nanoscale cues stimulate a filopodia-mediated response by cells, resulting in contact guidance and change in cell morphology on features as little as 10 nm [163]. Adherent and spread MSCs exhibited more prominent stress fibres and were more likely to undergo osteogenic differentiation compared to more rounded cells [146]. On 90 and 55 nm high islands, in vitro cytoskeletal formation and organization were more distinct than on planar surfaces [164]. On 10 and 25 μm wide grooves cells assumed polarized non-spread morphology and displayed downregulation of Rho and α-actin expression, leading to reduced cellular tension and reduced cellular signaling, while stress fibres and adhesion formation on 100 μm grooves appeared similar to planar controls, as an increased inter-ridge area allowed the cells to spread out and assume osteo-specific function [160]. Nanotopographies have also been shown to be disruptive to focal osteoblast adhesion formation in vitro [155,157], being especially pronounced on 120 nm wide nanopit topographies, when compared to nanocraters and nanoislands. Intriguingly, despite a general downregulation of focal adhesion formation by different nanocues, osteoblasts cultured on nanopits demonstrated a reduction in fundamental signaling pathways, while on nanocraters and nanoislands – enhanced expression of genes essential for osteogenesis. These findings indicate the complex relationship between nanocues, cell adhesions, cytoskeletal tension and cell differentiation.

In contrast, nanopattern pits 120 nm wide and 100 nm deep were found to be essential for osteogenic differentiation in the absence of other osteogenic factors. Compared to planar controls, square ordered (SQ) and completely random patterns, disordered square pits (displacement by up to 50 nm on either axis from their square position (DSQ50)) significantly augmented dense mesenchymal stem cell aggregation into bone nodules with elevated levels of osteocalcin, osteopontin and bone osteoid formation [41]. Subsequently, McMurray et al. demonstrated in vitro retention of skeletal stem cell markers at 8 weeks in cells cultured on SQ surfaces, while DSQ50 again elicited osteogenic cell differentiation [165]. Increased expression of osteocalcin and osteopontin after 21 days of cultures on nanotopographical surfaces in vitro [158] correlated with osteoblast differentiation timelines described by Lian and Stein [12]. Recently, nanocues were demonstrated to induce the activation of canonical signaling pathways, possibly indicating earlier stimulation of osteogenic differentiation [158]. Interestingly, nanotopographies did not inhibit endothelial differentiation [158] essential for neovascularization in de novo bone synthesis.

Cell adhesion to implant surfaces is mediated by extracellular matrix proteins [124]. Greater surface microtopography, and consequently greater surface area for fibrinogen adsorption, leads to enhanced platelet adhesion and activation, and potential up-regulation of osteogenic reactions in vitro [166,153]. Complex implant surfaces are more amenable to fibrin attachment, thus establishing the temporary osteoconductive matrix [10]. The association between surface texture, osteoconductive matrix formation and subsequent recruitment of osteogenic cells may be an important consideration in understanding the process of contact osteogenesis, de novo bone formation and in vivo implant integration. Nanotopography is currently receiving significant interest as a cue that can be patterned onto load-bearing devices for in vivo application.

2.2.5. Implant porosity

Implant porosity is essential for in vivo vascular formation, proliferation of mesenchymal cells and ultimately osteogenesis [167], and is key in facilitating successful osseointegration, as illustrated

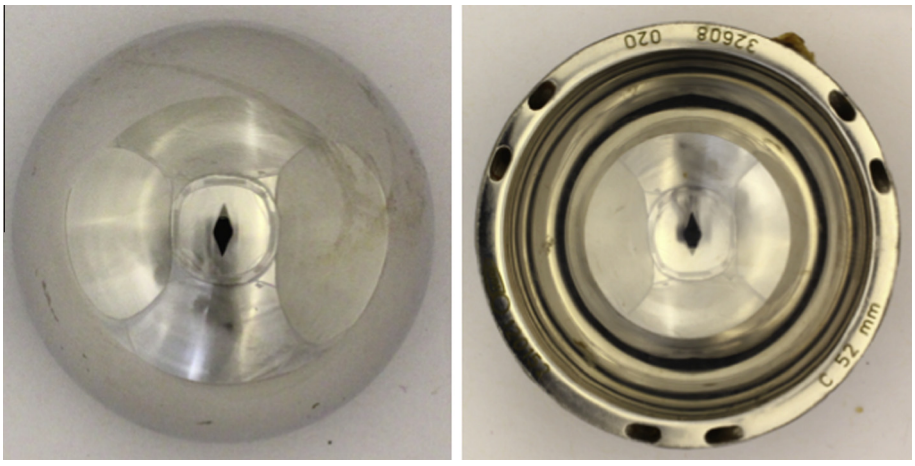

Fig. 3. (a) Retrieved large diameter Co–Cr femoral head and monobloc Co–Cr acetabular cup used in MoM bearing. (b) The RedLux height map of the head and cup, showing wear scars (purple) at 30° to the pole.

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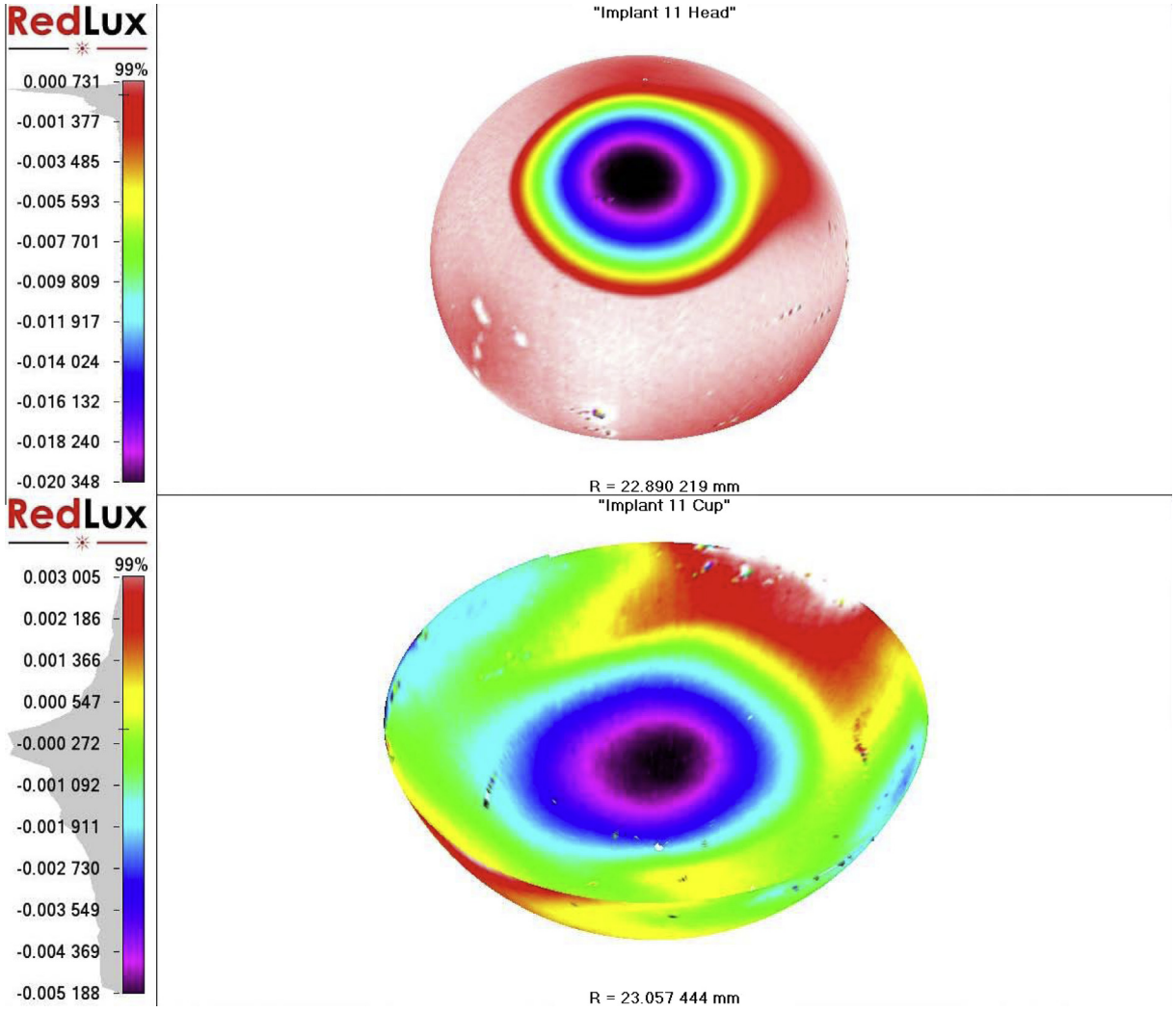

Fig. 3 (*continued*)

in Fig. 2. Trabecular metal (TM) is an example of a highly porous material, made of elemental tantalum, in clinical use [168]. Similarly to Ti, tantalum forms a passive oxide layer [168], which, on exposure to bodily fluids, adsorbs hydroxyl groups combining with calcium and phosphate to form apatite nucleation [169]. The 3-D structure of TM provides a continuous regular lattice of struts, allowing for interconnecting pores of consistent size and an overall porosity of 80% [170], enabling rapid bone ingrowth and enhanced interface shear strength in vivo [171]. Although the Young's modulus of tantalum is reasonably high, an inherent degree of flexibility in the structure of TM enables its stiffness to approach that of trabecular bone, thus facilitating physiologic load transfer [170]. Experimental models reveal that TM implants are only minimally less stable than cemented implants, even in the presence of significant bone defects filled with bone graft [172], resulting in, to date, good clinical implant survival [173,174], although long-term results are awaited given this is a new technology. Critically, there remains a paucity of evidence on the exact surface characterization of tantalum after fabrication.

3. Case report

The main perceived advantage, leading to the renewed interest in MoM bearing surfaces in hip arthroplasty in 1990s, was their

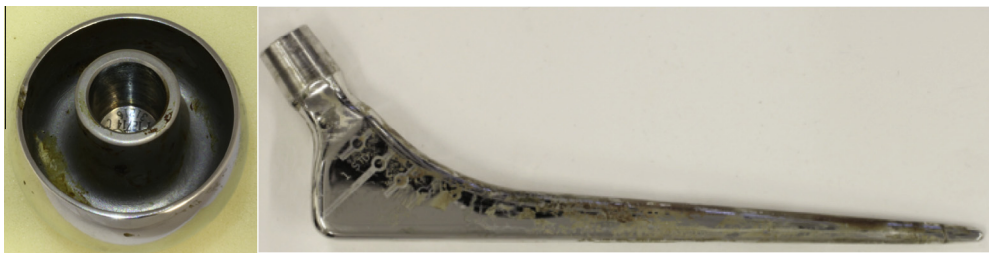

Fig. 4. (a) Retrieved large diameter Co–Cr femoral head taper, trunnion and the cemented stem. Wear-assisted corrosion damage is seen on the stem, likely disrupting stem–cement interface. (b) The RedLux height map of the taper showing wear scars (purple) in sub-polar regions where the trunnion engages. (c) The RedLux height map of the trunnion showing polar end damage.

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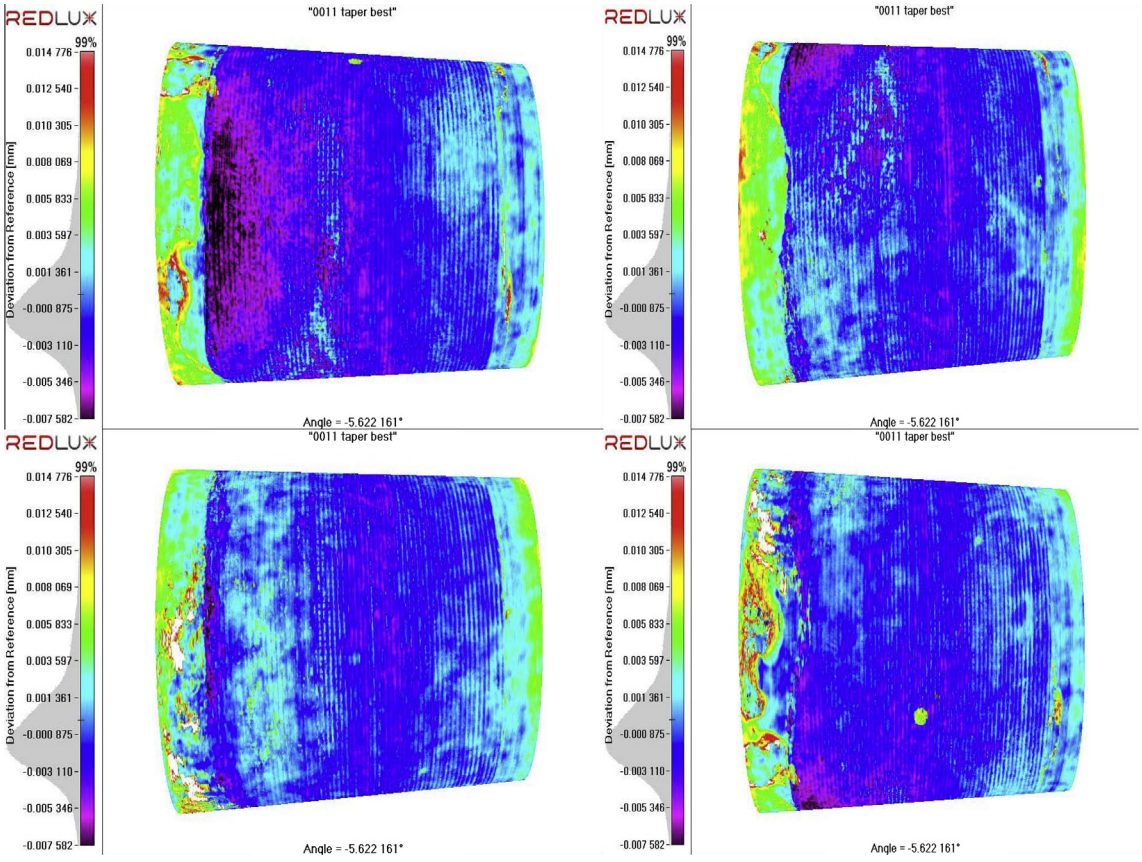

Fig. 4 (*continued*)

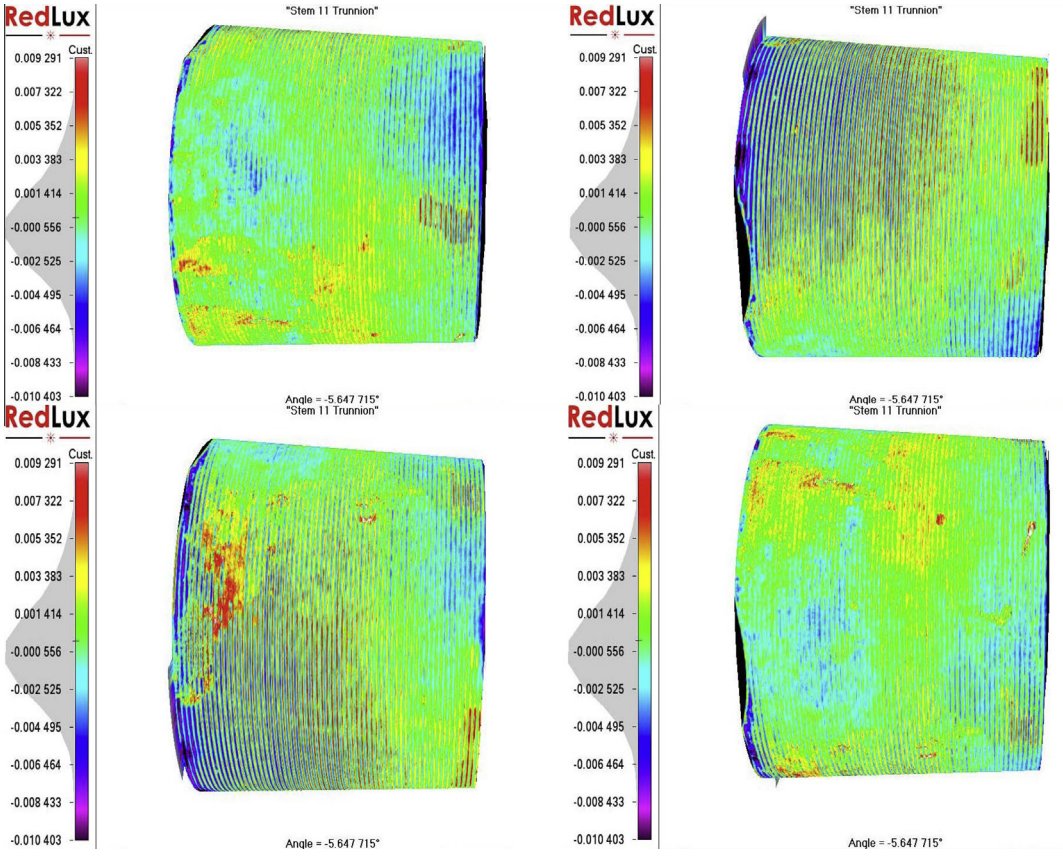

Fig. 4 (*continued*)

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Table 1
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reduced wear compared to metal-on-polymer alternatives [97]. Other advantages included bone stock conservation in resurfacings and greater stability due to the use of larger head sizes [97,175]. This was supported by promising mid-term clinical results [176]; however, recent evidence has demonstrated significant failure, local adverse reactions and systemic effects [2,97,177], triggered by metal debris generated from bearing surfaces or tapered junctions [97]. Asymptomatic MoM bearing hips may be associated with significantly elevated metal ion levels [97], and thus current clinical advice for patients with MoM implants in situ is to be reviewed yearly, with blood metal ion levels and hip magnetic resonance imaging (MRI) investigations [177].

A 64-year-old female had an uncomplicated primary hybrid MoM THR in 2004, with satisfactory radiographic examination. In 2010 the patient developed significant groin pain and radiographic assessment revealed evidence of acetabular loosening in zones 1, 2 and 3, and calcar bone resorption. Interestingly, inflammatory markers were normal and blood Co and Cr levels were 162 and 118 nmol l^{-1}, respectively, and while an MRI scan showed moderate fluid collection, hip joint aspiration revealed no evidence of infection (Co and Cr levels of 2510 nmol l^{-1} (148 ppb) and 1780 nmol l^{-1} (93 ppb)).

The patient underwent revision surgery using a ceramic-on-polyethylene bearing couple in 2012. Peri-operative cavitary acetabular bone defects, calcar erosions, brown joint fluid and tissue metallosis were seen at surgery. Histological examination of peri-operative samples revealed metallosis and moderate ALVAL. Post-operatively, the symptoms improved, and at 12 months the Co and Cr levels returned to normal (19 nmol l^{-1} (1 ppb) and 16 nmol l^{-1} (0.8 ppb). Non-contact 3-D metrological investigations of the retrieved implant surfaces were performed using an artificial hip joint profiler (RedLux, Southampton, UK). The analysis showed characteristic wear scars on the head and cup (Fig. 3a and b), and taper and trunnion (Fig. 4a–c), indicating the origin of wear particles. Mechanically assisted crevice corrosion at the head/neck junction was previously shown to be significant in MoM THR failures [98], generating wear particles that might be more harmful to the local soft tissues than those from the bearing surfaces [99]. While the volumetric wear decreases at the bearing surfaces with their increasing diameter, the metal ion release from the taper junction increases [98], the increased torque from larger bearing surfaces possibly contributing to the toggling and wear-assisted changes at the taper junction. The toggling created peaks in load at the open distal end of the taper junction, causing more pronounced damage, but the torque also triggered mechanically assisted changes more distally at the stem, generating a high metal ion and particle load. Therefore, a combination of corrosion and wear debris release discussed above resulted in the failure of primary THR requiring revision.

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4. Conclusion

In this paper we have reviewed aspects of osseointegration relevant to the orthopaedic practice (summarized in Table 1). It is important to note that only 33–62% bone–implant contact is achieved by modern titanium implants with commercially available surface treatments at 3–6 months [178], indicating opportunities for improvements in osseointegration through further research. Osseointegration is a complex process involving a number of distinct mechanisms affected by the implant bulk properties and surface characteristics. However, despite significant investments into bioengineering research, developments remain limited often as a consequence of non-standardization of approaches across the industry and field. The biological ageing of titanium facilitates the understanding of variation in initial host reactions post-implantation, and may aid in greater translation to wide clinical market application in orthopaedic prosthetics. In modern orthopaedic implant design, the choice of materials and their bulk properties, together with surface modifications including wettability, roughness, HA coating and porosity, have been carefully considered and implemented to result in improved clinical efficacy.

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Appendix A. Figures with essential color discrimination

Certain figures in this article, particularly Figs. 1–4 are difficult to interpret in black and white. The full color images can be found in the on-line version, at http://dx.doi.org/10.1016/j.actbio.2014.06.004.

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