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Ti6Al4V Surface Modification Techniques to Modulate Bone Cell Response: A Review

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Abstract

Biomaterial-tissue interactions are known to largely affect implant performance, relating to alteration of physiological processes. Within this context, metals continue to have a major role as most implants contain at least one metallic part. In particular, titanium alloys are of pivotal importance in orthopedics and dentistry. Being osteointegration somewhat affected by implant surface conditions, surface modification qualifies as a way to modulate tissue response, net of an effective design of the whole implant. Currently, a lack of full understanding on the direction to be taken for proper techniques and process conditions to be employed, for the regulation of osteointegration, can be recognized; this happens as a result of the inherent complexity involving host response, implant location as well as its surface chemistry, topography, stiffness and so on. This short review focuses on one of the most used titanium alloys, namely *Ti6Al4V*. An overview of viable surface modification processes studied in view of bone cell response, as a way to predict implant performance, will be provided, together with the most recent research findings towards a new generation of biomedical implants.

Keywords: Ti6Al4V; surface modification; bone cell;

1. Introduction

For an implanted device to fulfill the purpose of its ideation, several factors must be taken into account, which can be managed to a limited extent, such as: (i) overall implant design; (ii) surgical procedure; (iii) patient conditions.

Due to the complexity of the problem and the presence of many confounding variables, reaching an optimum implant configuration is a major issue and significant effort has to be put to solve many inconveniences, which eventually terminate to implant failure and aggravation of patient health.

Several classes of materials are today employed for biomedical devices, but metals still have a major role, in particular for applications requiring immediate structural support. Unfortunately, in cases involving for example critical patient conditions, metal sensitivity [1] or invasive surgical procedure [2] the chances of failure increase dramatically. To help preventing the consequences of above-mentioned drawbacks, an action to modify biomedical device features can be performed.

Focusing on implant design, its macro- to nano-scale features need to be properly tailored. For a fixed material, the shape of the implant, more or less complex based on limitations of involved processes, provides its global stiffness. Also, surface and subsurface properties strongly affect local tissue response. In fact, it is acknowledged that bone-implant interface can be subjected to significant changes by only modifying surface composition, texture and energy. [3]

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Both manufacturing and secondary processes mark surface texture, microstructure, chemistry, residual stress state, comprehensive part functionality and endurance in severe conditions given by body environment. Thus, the entire production chain must necessarily balance diverse requirements.

Within metallic alloys, titanium ones are pivotal to certain applications ranging from, but not limited to, orthopedics to dentistry [4] for advantages such as their high strength-to-weight ratio and spontaneous passivation with highly biocompatible oxides. *Ti6Al4V* alloy has been and is widely employed but endurance and bioresponse of devices are still troublesome, partly because of the toxic effects of *Al* and *V* elements [5].

In the past years several surface modification techniques have been developed to provide superior biomedical device performances, involving distinct mechanisms and primary sources. This work will focus on surface modification of *Ti6Al4V* parts performed in the last five years and early-stage testing results based on *in vitro* cell response as a preliminary assessment before *in vivo* testing, with related limitations.

Cells as basic units of living organisms are sensitive to multiple cues from surrounding environment. In culture, substrate mechanical properties, microstructure, topography and chemistry can affect protein adsorption (key to cell sensitivity) and cell attachment, spreading, differentiation and proliferation. Being distinct types of cells involved in bone development and remodeling and cell response strictly related to its type and culturing conditions, the analysis and discussion of outcomes will be restricted to osteoblasts and osteoblast-like ones.

2. Surface Modification Approaches

Several primary processes can be involved to obtain a semi-finished product to be subsequentially treated through secondary processes. As stated in the introduction, part properties and functioning are a result of source material, manufacturing method, primary and secondary processing conditions. Not only in industrial practice but also in preliminary assessments, primary processes involved are distinct: typical tested samples are machined out of extruded rods, rolled sheets, cast or additively manufactured (AM) (typically employing electron beam melting EBM or selective laser sintering SLS) from metallic powder to the desired shape to be further treated. If intermediate treatments such as heat- or high pressure-based ones are not performed to bring manufactured samples to a reference metallurgical state, starting sample properties may be notably different and affect outcomes from subsequential processes [6] thus it is an important issue to be taken into consideration.

Techniques employed for surface modification of *Ti6Al4V* defined by the following mechanisms will be mainly covered in the next paragraphs: (i) mechanical deformation, (ii) chemical reactions, (iii) thermal sources. Additionally, deposition techniques (which partially overlap with previously mentioned ones) and biological modification will be briefly introduced but no further analysed. Categorization of techniques is mainly based on primary source/mechanism type. Nevertheless, it needs to be pointed out that each process which will be discussed may encompass more than a single modification mechanism (sometimes involving deposition of a film on the surface) as it is hardly possible to alter, for example, topography without affecting microstructure and chemistry.

2.1. Mechanical Processes

Within mechanical-based processes, some of the most used pertain to abrasive machining. They owe their name to the utilization of high quantity of hard and sharp, mostly irregularly shaped, particles as tools for material removal. As a result of processing, grooves or randomly distributed craters, with dimension related to abrasive size, may be generated on the treated surface, the former for grinding and polishing, the latter for grit-blasting, as illustrated in Figure 1 a) and b). [7] These techniques, together with surface topography alteration, according to processing conditions, may introduce a more or less pronounced strain hardening together with grain distortion and chemical alteration due to elements in the abrasives. The latter applies mostly for grit-blasting, which is generally performed delivering Al_2O_3 [8] particles at high speed onto part surface.

Grinding and polishing in biomedical applications are generally employed with the aim to smooth surface [9], which has been found to be beneficial in certain cases, for example in easing revision surgery and implant removal due to bony on growth reduction [10] but they can also be employed as a preliminary operation in view of further processing [11] or as a reference for comparing different processing methodologies. In [12] ground sheets have been compared to as built AM ones to assess the effects of surface roughness and Cu-loading on osteoblast response.

In [13] polished and electron beam modified disks have been compared for coating adhesion and osteoblast activity while in [14] samples were ground to remove the effects of previous operations for subsequent anodic and plasma treatments. Grit-blasting is often employed to roughen implant surface and increase contact area to accommodate cells and to modify wettability [8] but also to remove undesired surface features such as residuals of unmelted powder from AM parts. By using specific blasting media, surface composition can be altered to some extent, for example when the same printing powder is used to treat AM components [9] or to purposely introduce highly biocompatible elements such as calcium phosphates [15].

Among material removal processes, milling, which involves a rotating cutting tool to remove layers of material, is frequently used to define the final shape of the implant starting from previously mentioned primary processes as in [16] where cast and milled disks were compared against SLS ones. Milling is widely used before further processing as in [17] where grit-blasting and ion beam implantation were performed. Nevertheless, milling alone also offers a peculiar surface texture (Figure 1 c) and, according to machining conditions, the presence of a hardened layer.

Furthermore, sliding friction treatment, which involves repeated sliding of a hardened tool against part surface is generating interest. In fact, it leaves plow marks on the surface and can bring surface roughness to values comparable to polished one but simultaneously introducing grain refinement up to nano-size [18].

2.2. Thermal Processes

Processes of interest involving thermal sources can be recognized in electrical discharge machining (EDM), laser, plasma and electron/ion beam treatments. EDM is based on erosion of conductive surfaces through subsequent electrical discharges generated between a properly shaped conductive tool-electrode and the workpiece, submerged in a dielectric fluid and powered by a generator. It has been largely employed to machine complex shaped components and create otherwise difficult slots [7]. Recently [19], the process has raised interest because of the possibility, through material melting, vaporization and removal, to obtain a wider range of microstructural and chemical variations (also involving elements from tool and dielectric fluid) and the creation of non-directional surface textures (Figure 1 d) to provide the implant with improved performance. In fact, by properly selecting tool-electrode material antibacterial effect might be introduced (e.g. through copper tools) but also enhanced osteointegration by processing the material with special powders mixed with the dielectric fluid (e.g. calcium phosphates).

Laser-based surface treatments make use of a coherent light beam to focus high density energy onto workpiece surface. According to source type and processing conditions, the effects of the process on component properties may be tuned from considerable to negligible based on requirements, for instance through ultra-short pulses in the order of pico- or femtosecond [20]. It is a highly versatile process enabling to produce specific surface textures towards performance optimization e.g. the introduction of directional textures to control cell attachment and spreading [21].

In electron beam and ion beam machining (EBM, IBM) the source of energy is a beam of electrons and ions, respectively, accelerated and focused on the surface to be treated. They might have similar applications as laser-based ones but with limitations given by the need of a vacuum chamber. Electron beam surface treatment makes it possible to modify both surface topography, microstructure and, with it, surface energy [13]. Ion beam processes find an interesting variation in ion beam implantation which allows ions to penetrate into part surface and modifying its mechanical and chemical properties [17].

Finally, plasma-based processes involve ionized gas used to bombard workpiece surface and by varying process parameters and gas type it allows to modify or leave unchanged surface topography and chemical composition. In [14] rutile-dense surface structure has been generated while in [22] the effect of plasma processing were not as marked with respect to untreated samples. As previously stated, plasma processing can also simply be used to remove contaminants and obtain super hydrophilic surfaces without modifying chemical composition and texture [15].

2.3. Chemical Processes

Chemical processing involves use of chemical reagents, such as acids or alkaline ones, to attack and dissolve material on surfaces in a controlled way.

These processes are frequently employed in combination with each other or mechanical/thermal processes. One typical application is to combine grit-blasting with acid etching sometimes performing further alkaline treatment to produce a hierarchical micro-to-nano structured surface to increase bone-implant contact area and regulate cell behavior [11]. In [8] HF and HNO_3 chemical treatment was performed to smooth surfaces generated from EBM process.

Chemical treatment is also performed as a preliminary preparation for further chemical modification or deposition. For instance in [23] *Ti6Al4V* sheets were treated with sulfuric acid, hydrogen peroxide, ammonia and hydrochloric acid in different combinations prior to modification with self-assembled monolayers while in [24] acid etching was used to prepare surfaces for subsequent composite coating deposition.

Nevertheless, surface chemical alteration, and in particular carbon content, apart from the reagent employed is strongly affected by processing atmosphere [15] and requires further control.

2.4. Deposition, Drug Entrapment, Biological Modification

Deposition and biological techniques are widespread and virtually infinite, they give the possibility to anchor extra components to surfaces to tailor not only biological interactions or place a barrier between metallic implant and body environment but, in particular for coatings, to simultaneously improve mechanical and tribocorrosion behavior. Plasma-based processes such microarc oxidation can be employed to create porous oxide coatings and hierarchical structures and decrease the surface content of toxic ions according to processing environment and conditions. In [5] selective removal of *Al* and *V* ions was noted into produced oxide coatings while in [25] surface was covered by multilevel porous structure and a bioactive calcium phosphate coating.

Electrochemical procedures are of interest for the deposition of porous highly biocompatible films such as chitosan/hydroxyapatite composite [24]. Self-assembled monolayers (SAMs) of molecules can be chemically deposited with the aim to provide surfaces with hybrid wettability properties [23]. Some techniques conventionally used to perform material removal, with proper modification allow coating deposition such as powder mixed EDM performed using , for example, hydroxyapatite particles as additives to dielectric fluid [19].

Drug entrapment can also be performed while depositing material onto implant surface in order to reduce systemic delivery of pharmaceutical agents. Biological modification involves immobilization of biological entities onto implant

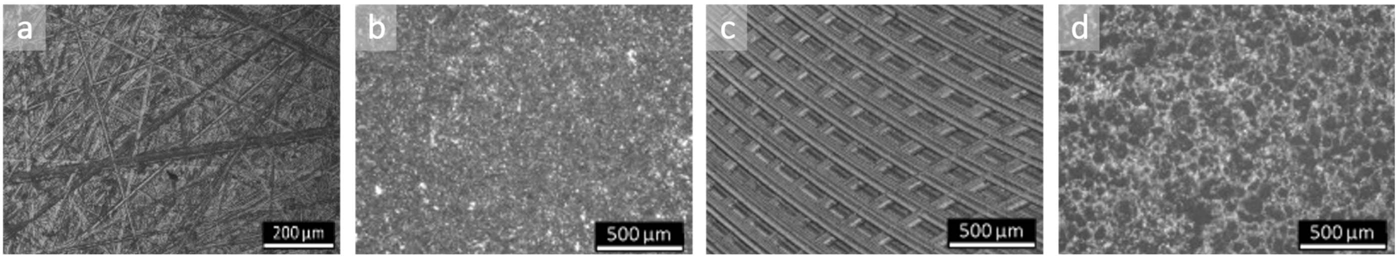

Fig. 1. Examples of surface textures after different secondary processes on *Ti6Al4V*: a) grinding, b) grit-blasting, c) face-milling and d) electrical discharge machining.

surface and it needs careful account for bond stability in aggressive environment. [3]

3. Processes and Cell response

Each of the processes covered in previous paragraphs potentially introduces more than one variation into implant surface and subsurface layers thus identification of affected properties is the core of a proper reading of results from biological tests. Referring to osteoblasts and osteoblast-like cells, their response to substrates is typically studied, apart through viability assays, analysing: (i) attachment, (ii) spreading, (iii) proliferation, (iv) migration, (v) matrix formation and mineralization [26].

Multiple works report comparison between reference ground, polished or machined samples and other surfaces modified with other mechanical, thermal and chemical processes in view of the previously mentioned assays but a comprehensive evaluation of contributory factors is rarely found. Those showing the most exhaustive analysis will be reported in the following lines.

For starters, in [9] laser powder bed fusion (L-PBF) manufactured samples subjected to mechanical processes as polishing and blasting are compared to as printed ones, in an attempt to contextually perform surface texturing without involving secondary processes by directly printing particular surface features on the surface. The comparison has been performed trying to minimize chemical changes during processing, grit-blasting has indeed been performed employing the same metallic powder used in printing phase. Obtained mean surface roughness for blasted and as built samples (with and without sprouts-like surface features) passed from Ra=3.2 µm and Rz=22.6 µm up to Ra= 9.9 µm and Rz= 65.1 µm thus reaching the meso-scale. Results in terms of cell proliferation and differentiation did not show significant differences between rougher as printed samples as micro-to-nano scale features have not been altered by the printed texture, thus finding it unsuitable to perform this kind of modification with the aim to influence cell behavior, because of resolution limitations of this specific manufacturing technology. Still, further analysis on cell matrix and implant fixation should be performed to assess the effects on higher scale. Nevertheless, one more thing should be considered while performing these evaluations: introduction of surface irregularities brings to detrimental effects on mechanical performance (especially fatigue).

In [20] and [21] different laser sources and processing conditions have been used to produce various types of surface textures. In [20] stochastic pillared structures and sinusoid periodic microstructures have been produced in the microscale and compared to laser-induced periodic structures (LIPSS) on the nanoscale and polished reference. Areal surface roughness difference between nanostructured samples and reference is minor while two orders of magnitude separate microtextured and polished ones. Contact angle of microtextured samples is almost halved with respect to reference while showing more interesting variations on LIPSS ones, with strong similarities to reference for one type and near zero contact angle value for another. These changes are only theoretically explained by the authors, relating to different irradiated energy and LIPSS regularity but not experimentally verified (no chemical characterization). Still, cell behavior in terms of cell adherence, spreading and migration follows roughness trends showing more limitations for cells to align and spread along microstructures with respect to nano-ones and reference. In [21] laser-processed samples showed micro-to-nano variations in texture, with microroughness being 2.8 to 7.5 times higher compared to polished reference and nano-roughness results more than doubled. From chemical (EDS) evaluation, composition has been found to be the same while approaching treated surface the presence of additional harder microstructural phases is found. Biocompatibility revealed to be higher for the roughest sample (*Ra*=3.37 μm), this occurrence was justified by the authors with overriding effect of improved surface area and thus protein adsorption which improves cell behavior, not experimentally evaluating, for example, different surface energy and residual stresses within tested samples.

In [18] it has been studied how sliding friction treatment might improve protein adsorption, cell spreading and differentiation, with virtually no change in surface roughness. In fact, the most significant variations are given by grain size, decreasing from micro to nano and increasing surface energy and, possibly, improving naturally formed passive layer uniformity.

In [11] polished, grit-blasted, acid etched and alkali treated samples, with a combination of these techniques, have been compared. Grit-blasted acid etched samples, with and without alkali treatment, shown hierarchical micro-to-nano pitted structure, the highest surface roughness and comparable contact angle with respect to polished reference. The highest hydrophilicity (almost halved contact angle) is given by polished alkali treated samples. Nevertheless, alkali treated samples outperformed the remaining in terms of cell proliferation mainly due to their three-dimensional nanonetwork added on starting surface, being it either smooth or textured.

4. Discussion and Conclusion

From the analysed limited literature, several weak points can be recognized in the works performed on analysis of osteoblast and osteoblast-like response to functionalized surfaces. In fact, as stated before, several factors of influence exist and need to be carefully considered when drawing conclusions.

In several works, certain aspects to which cells are sensitive are not brought up or they are merely mentioned but not experimentally explored, with some of them interrelated and listed hereafter: (i) chemical composition; (ii) surface energy, its variation with implant storage time and ranges of contact angle actually influencing mechanisms like protein adsorption; (iii) proper description of surface texture using more effective indicators than *Ra* and *Rz*; (iv) microstructure effect on the release of substances from implant to body environment; (v) residual stresses.

Furthermore, from the use of osteoblast and osteoblast-like cells having different sources and variations in culture conditions, higher dispersion and even contrasting results may be achieved. In addition, surface modification processes affect mechanical performance of implants, as well as tribocorrosion behavior and fatigue resistance; these assays need to be further integrated with biological tests and systematized.

Thus, at the current stage, being multiple mechanisms still a matter of disagreement, general guidelines on which production chain is best suited for bone cell behavior modulation cannot be drawn.

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