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REVIEW ARTICLE

Structural influence from calcium phosphate coatings and its possible effect on enhanced bone integration

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Abstract

Objective. The aim of this review was to summarize our present knowledge about calcium phosphate (CaP) coatings on implants with respect to their topographical appearance at micrometer as well as nanometer level and also the reported influence on bone healing. ***Material and methods.*** The PubMed database was used with the key words – surface roughness, CaP coating, implant, bone integration, clinical studies, experimental studies – used in different combinations. Only *in vivo* studies were taken into consideration. ***Conclusions.*** A significantly improved healing capacity associated with CaP-coated implants is often reported, but individual importance of the several modes of surface changes introduced, deliberately or not, is usually very difficult to interpret. Several studies claim this difference to be due to altered chemistry, but in many the result may equally well be dependent on the surface topography. The few studies that have been published indicate that nanometer structures have an impact on early bone healing. However, the optimal size and distribution of nanometer-sized particles or pores applied on implant surfaces is still unknown, as are the evaluation effects of micrometer roughness. Improved surface characterization is needed if we are to reveal effects dependent on isolated nanometer alterations.

Key Words: *Calcium phosphate coating, implant, surface topography*

Introduction

Since the beginning of the 1980s, surface structure has been identified as one of six factors particularly important for implant incorporation in bone [1]. Faster and stronger bone formation may mean better stability during the healing process, thus permitting more rapid loading of the implant.

Several reviews published during the past 10 years have concluded that implant surface roughness on a micrometer level influences cell and tissue response [2–4]. A possible influence from nanometer roughness has been indicated, but more studies are needed before this can be verified. Admittedly, there are many *in vitro* studies allegedly supporting the importance of nano-roughness for the bone response, but *in vitro* studies lack *in vivo* characteristics such as the delicate balance between osteoblasts and osteoclasts. Furthermore, vascular, hormonal, and loading influences are lacking in the *in vitro* environment, making it too artificial for any reliable conclusions to be drawn with respect to generalization of results of the *in vivo* situation. The few *in vivo* studies supporting the notion that nano-roughness is of substantial importance for implant incorporation suffer from either artificial study designs or poor control of the influence of other topographical or non-topographical surface parameters. Therefore, at the present level of knowledge, whether or not nano-roughness is important for the tissue response to clinical oral implant remains unknown. It is possible that the discrete changes reported *in vivo* will in fact be so dominated by surface micro-roughness in clinical reality that the nano-indentations play no significant role (Figure 1A, B).

It is also clear from the articles reviewed that the exact role of chemistry and topography on the early events of bone integration is still poorly understood. In research on oral implants, machined surfaces have been used synonymously with a Brånemark-turned implant without any consideration of the particular turning process applied for this implant. Thus, very different surfaces have been used as "machined" controls when investigating new and rougher

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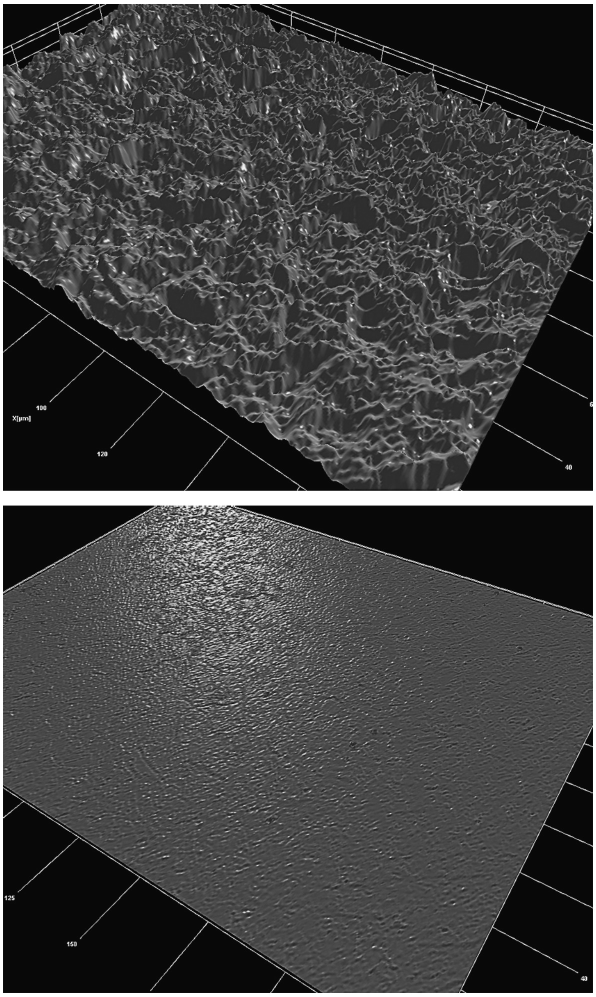

Figure 1. A. Computer image illustrating surface roughness on a micrometer scale, which is a scale usually used when evaluating surface roughness and its effect on biological processes. B. Computer image illustrating surface roughness on a nanometer scale, when the micrometer roughness has been removed by a Gaussian filter. The image represents the same measurement as in A, except that the filtering process is different.

surfaces. From time to time, ceramic surfaces have been in focus in the scientific literature as being a promising solution for rapid integration in the bone tissue. Hydroxyapatite-coated implants have been launched and, more recently, surface configurations on zirconia implants have been found to result in a similar bone response as for titanium implants [5,6].

An increasing number of surface modifications have been introduced, and even though there have been a large number of studies comparing "machined" surfaces with new, roughened surfaces, our knowledge about whether, in general, one surface modification is better than another is still lacking. To add further to the confusion, not only does surface topography change with different manufacturing techniques, the surface chemistry and physics may also be changed, albeit accidentally. So far, coating with hydroxyapatite or other calcium phosphate (CaP) compositions is the most investigated surface modification altering both chemistry and topography. These studies often tend to consider the topography to be more or less similar and that the coating technique principally will change the chemistry. This review summarizes our present knowledge about CaP coatings and their topographical appearance on the micrometer and nanometer levels, as well as the reported biological influence of CaP on bone healing.

Topographical description

Albrektsson & Wennerberg [7] suggested that smooth surfaces have an Sa value (for definition, see below) of <0.5 µm, minimally rough surfaces 0.5–1.0 µm, moderately rough surfaces 1.0–2.0 µm, and rough surfaces >2.0 µm. They also concluded that height descriptive parameters in combination with spatial, hybrid, or functional parameters, preferably in three dimensions, would be a much better characterization of modern implant surfaces. Even though different parameters are referred to in the reviewed articles, the great majority are only height descriptive and the discussion is almost always centered on the Ra or Sa value. It is therefore possible to compare different studies based on such parameters alone.

However, since there is still some confusion about the most commonly used height-descriptive parameters, namely Ra and Sa, here is a short description: Ra is the arithmetic mean deviation of a profile and is a robust and stable height descriptive parameter. Sa is the arithmetic mean deviation of a surface. Since the mean height deviation is based on so much more data than Ra is, Sa is an even more stable height descriptive parameter (Figure 2).

Bone response dependent on surface chemistry and physics

It is clear from several studies that surface chemistry and/or physics may influence bone response similarly to topographical changes [7–10], even though it may be difficult to study the individual influences of topography, chemistry, and physics in a controlled manner, since these may be altered simultaneously by accident. Ellingsen et al. [8] decreased the surface topography of blasted implants with an etching process, from the blasted implants an ordinary Sa of 1.1 µm to 0.9 µm, yet they demonstrated stronger bone responses. Whether or not this was dependent on the small amounts of fluoride ions (i.e. a chemical influence), the increased nano-roughness, or other surface characteristics of the OsseoSpeed™ surface is unknown. Sul et al. [10] compared removal torques of similarly designed Osseotite, TiUnite, and experimental Mg implants that had 0.68, 1.2, and 0.78 µm, respectively, in Sa roughness, yet the experimental Mg implant demonstrated the strongest bone response, possibly dependent on Mg ions

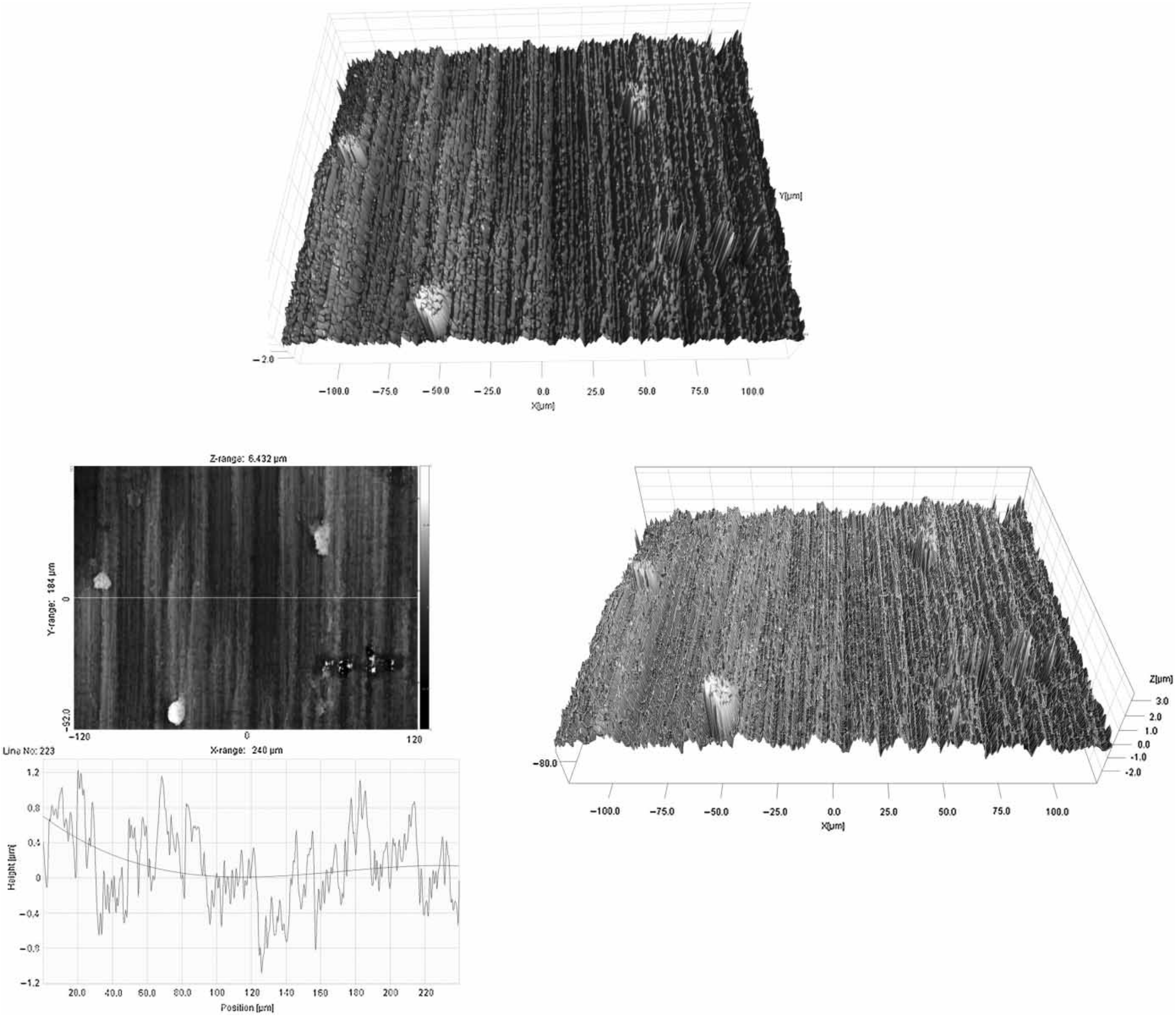

Figure 2. The original measurement (above); below to the right, a profile from the measurement illustrating the source of parameter Ra, i.e. a two-dimensional parameter; below to the left, a three-dimensional evaluation representing the parameter Sa. The Sa parameter includes much more data than the Ra and is therefore more stable and reliable when evaluating the average height deviation.

acting as catalysts, i.e. a chemical effect. The Buser et al. study [9] demonstrating stronger bone responses to a new surface with high surface energy may be attributable to this change, but as found in another study the same hydrophilic surface likewise had an altered micro-roughness in terms of surface enlargement as well as an altered nano-roughness compared to the controls [11]. Hence, in an individual experiment it is usually difficult to claim with certainty what really causes an increased bone response to a given surface, since so many parameters may have changed. This is true also for hydroxylapatite-coated (HA) implants, where the coating process changes the chemistry by adding HA, but simultaneously may alter micro- as well as nano-roughness and, depending on the precise process of application of HA, potentially influencing surface physics as well. With these shortcomings in reliably interpreting the reason for stronger bone responses in mind, we considered it timely to summarize some experimental data on HA-coated implants, since this chemical alteration of oral implants has been investigated in many studies spanning over a long period of time.

Bone response to CaP coatings: micrometer level

A coat applied to an implant surface changes the outermost surface material totally, but the influence on surface topography may be considerable as well. In the present review, we concentrated on topographical changes rather than chemical changes. To collect relevant articles, a database (PubMed) was used with the following key words used in different combinations – surface roughness, CaP coating, implant, bone integration, clinical studies, experimental studies. Only *in vivo* studies were included in the present review.

In many studies investigating different surface modifications, a positive correlation has been found between surface roughness and osseo-integration, and, in many, although not all, of these studies the roughest surface investigated was the CaP coat.

Wong et al. [12] compared different surface modifications in a pig model, i.e. measuring roughness with a stylus. Ra for the machined implant was 1.5 μm, for the blasted implant 2.3 μm, for the blasted + etched implant 1.9 μm, and for the HA-coated implant 6 μm. Topographical data indicate greatest roughness of the HA-coated implants, even though precise raw values of this study are not comparable to those of investigators with a more precise description of the technique. This latter comment applies in the case of many of the quoted studies in this reading. However, push-out tests after 12 weeks demonstrated a strong correlation with increasing roughness and interfacial strength.

In studies by Gotfredsen et al. [13] and Gottlander et al. [14], a change from minimal roughness to moderate roughness has been found to result in stronger bone responses. Gotfredsen et al. [13] compared machined (Sa 0.31 μm), blasted (Sa 0.61 μm), and HA coated implants (Sa 1.89 μm) in a rabbit model. The topography was measured with a confocal laser profilometer. After 3 and 12 weeks, the blasted implants required significantly more removal torque than the machined implants, with the HA-coated implants requiring the highest removal torque. Gottlander et al. [14] compared CaP-coated with uncoated titanium implants. The topography was measured with confocal laser profilometry. The uncoated Ti implants had an Sa of 0.53 μm and the coated implants an Sa of 1.42 μm. More bone to implant contact was found after 4 weeks in rabbits for the coated implants, while after 6 months there was no difference.

Vercaigne et al. [15] compared machined, titanium plasma-spray (TPS) coat, TPS + acid etched, and TPS + HA. The Ra was 0.35, 2.39, 2.59, and 3.31 μm, respectively. The surfaces were measured with a confocal profilometer. In goat bone, a significantly higher amount of bone-to-implant contact was found for the roughest HA-coated TPS surface after 3 months. Li [16] found an increase from smooth-to-moderate roughness to be advantageous when he inserted four different surface modifications of cylinders into rabbit bone: commercially pure titanium (c.p. Ti), pressed titanium oxide, pressed Ti/HA, and HA. The surface roughness was measured with a mechanical stylus and Ra value for c.p. Ti was 0.61 μm, for titanium oxide 0.42 μm, for Ti/HA 0.53 μm, and for HA 1.50 μm. HA demonstrated the strongest bonding strength after 1–3 months.

As has been indicated above, CaP surfaces have not always been the roughest, nor demonstrated the strongest bone response. Yeo et al. [17] compared calcium metaphosphate (CMP) coated, anodic oxidized, HA particle blasted and turned implants in a rabbit model. The follow-up times were 2 and 6 weeks; thereafter the implants were investigated with resonance frequency and removal torque. The different surface topographies were measured with an interferometer. Ra for the turned implants was 0.5 μm; the corresponding values for the CMP-coated, anodized, and blasted implants were 0.7, 1.4, and 0.9 μm, respectively. After 6 weeks the anodized implants demonstrated significantly higher removal torque than the turned implants. No other statistically significant differences were observed even though all surface modifications had a higher removal torque than the turned implants. However, all investigated surfaces except the CaP-coated ones were minimally rough and, in the case of the turned surface, very close to being classified as smooth.

In other studies, the possible influence from an increased surface roughness is difficult to extract from the results. Blasted and sintered titanium implants with and without CaP coating were studied by Hayakawa et al. [18]. Implants were inserted in rabbits and evaluated after 3, 4, and 12 weeks. A mechanical stylus was used for topographical characterization. The blasted Ti implants had an Ra value of 1.3 μm and the sintered samples an Ra of 14.1 μm. No measurements were taken after the CaP coating process. After 12 weeks the sintered implants with a CaP coat demonstrated the highest amount of bone to implant contact. No differences were found at any of the other time-points.

Vercaigne et al. [19] compared TiO_2 blasted implants with and without three different thicknesses of CaP coats. The surface topography was claimed to have been measured with an optical profilometer; however, no values were presented in their publication, only references to a previously published paper. The implants were inserted in goats for 6 and 12 weeks. The thickest coat, 4 μm, demonstrated the strongest bone integration. A CaP coat was also investigated by Hayakawa et al. [20]. In this study, a comparison was made between as-machined with and without a CaP coat and grit-blasted implants with and without a CaP coat. A mechanical stylus was used to measure the grit-blasted surface, which was claimed to have an Ra value of 4–5 μm. No further topographical information was given for this or any other of the investigated implants. After 12 weeks, the rough-coated implants in rabbits demonstrated stronger bone anchorage compared with coated, smooth samples. The rough grit-blasted implants showed a stronger bone response than as-machined titanium implants. CaP-coated smooth implants demonstrated more bone in contact with the implant than the uncoated smooth implants. No difference was found between grit-blasted implants with or without coating. With a lack of proper topographical characterization, it is impossible to interpret the possible effects from increasing the roughness of the implants. Novaes et al. [21] inserted four different surface modifications in a dog model: machined, TPS, HA, and sandblasted with soluble particles (tricalcium phosphate). After 3 months, the sand-blasted surfaces demonstrated significantly stronger bone-to-implant contact than the machined implants, a finding claimed to be related to the allegedly superior surface of the sand-blasted implants. However, no topographical measurements were presented. The authors only refer to information from the producer of the sandblasted surface, who claimed it to be 250% rougher than machined or etched surfaces. Lee et al. [22] compared calcium and phosphate films electron-beam evaporated on the surfaces (Ca/P ratio 1.62) with as-machined and as-blasted implants. Topographical evaluation was performed with a scanning electron microscope (SEM), thus only a surface morphological description was provided. Mechanical and histological investigations were done after 12 weeks in rabbits. Similar results were achieved for the blasted and coated implants, with both these surface modifications exhibiting a stronger bone response than the as-machined surface. There may have been a correlation between surface roughness and bone integration in this study.

In some studies, a negative correlation between increasing roughness and bone formation is reported. Borsari et al. [23] compared the osseo-integration of grit-blasted titanium rods with and without hydroxyapatite coating. The Ra was 18 μm for the titanium implants and 12 μm for the coated implants. After 3 months in sheep tibia, no differences between the two surface modifications were found in cortical bone, but in trabecular bone a significantly improved osseo-integration was noted for the coated implants. In this study, it is difficult to separate the influence of chemistry and topography, but with respect to topography a negative correlation between increasing roughness and bone integration was found. The coated surface may have been too rough.

Savarino et al. [24] compared two different roughnesses achieved by an unknown machining method; Ra was 5.9 μm and 22.5 μm, respectively. The technique used for surface measurements was not described. These two surfaces were used with and without a fluor-hydroxyapatite coating, resulting in a decrease of Ra to 5.6 μm and 21.2 μm, respectively. The two uncoated groups achieved a higher degree of bone mineralization than the coated, and the least rough surface demonstrated the highest amount of bone-to-implant contact calculated from histological sections.

Aebli et al. [25] investigated two different implants with the same surface roughness, Ra 30 μm measured with optical profilometry. The two different surfaces were grit-blasted with and without HA plasma sprayed coating. There were no differences in interfacial strength after 1, 2, and 4 weeks. More bone was found after 4 weeks for the HA-coated implants, which was indicative of a possible chemical influence on bone formation.

Le Guehennec et al. [26] compared titanium implants blasted with aluminium, blasted with CaP with and without a CaP coat, and sandblasted + etched (SLA) surfaces in a rabbit model. Surface roughness was measured with a mechanical profilometer. The Sa value for the Al-blasted Ti was 2.12 μm; the CaP-blasted had an Sa of 2.61 μm, the CaP-blasted and CaP-coated had Sa values of 0.88 μm, and SLA an Sa of 1.98 μm. The SLA and the CaP-coated implants demonstrated significantly more bone-to-implant contact compared with the Al-blasted Ti after 2 weeks in rabbit bone. After 8 weeks, no difference was found between the four surfaces. There was no correlation between increasing roughness and bone integration. From a roughness point of view, the result confirms the hypothesis that moderately and minimally rough surfaces present stronger bone responses than rough surfaces.

Taba et al. [27] compared bone density by a radiographic evaluation in a dog model. Machined, TPS, HA-coated, and sandblasted implants with soluble particles under unloaded conditions were compared. After 3 months, no significant difference was found between the different surfaces. No topographical evaluation was presented.

Not just c.p. titanium but also titanium alloys have been coated with CaP. Svehla et al. [28] investigated polished Ti_6Al_4V, grit-blasted Ti_6Al_4V with and without plasma-sprayed HA coating, and plasma-sprayed titanium with and without HA coating. The HA coating had different thicknesses up to 150 μm. Ra differed from about 0.2 μm to 15 μm judged from a figure in the paper. A thicker HA coat on the grit-blasted implants resulted in greater Ra value, while a thicker HA coat on the plasma-sprayed implants resulted in a decreased Ra value. The polished titanium alloy demonstrated the smoothest surface. All plasma-sprayed implants had a higher Ra value than any of the grit-blasted implants. After 4, 8, 12, and 26 weeks the plasma-sprayed implants demonstrated higher shear strength compared with the grit-blasted implants. Fini et al. [29] investigated Ti_6Al_4V implants with two roughnesses achieved with a titanium bond coat. These two surface modifications were used with and without fluor-hydroxyapatite coating. Ra was presented but no information was given as to how the values were determined. Ra for the smooth Ti implant was 5.9 μm and for the smooth implant with HA coat 5.6 μm. Rough Ti had an Ra of 22.5 μm and rough titanium + coat an Ra of 21.2 μm. Bone-to-implant measurement after 12 weeks in sheep was evaluated. The lowest roughness demonstrated the significantly strongest bone response. The result can be interpreted as if the chemistry is a dominant factor, but another possible explanation is that the surfaces in the study simply were too rough for any optimal bone response.

Human bone

Goené et al. [30] inserted micro implants in human maxilla and compared dual-etched surfaces with and without nanometer CaP coating. SEM was the only method used to characterize the implant surfaces. After 4 and 8 weeks, significantly more bone was in contact with the etched surface.

In a randomized, controlled, clinical study, Jeffcoat et al. [31] found that HA-coated cylindrical implants resulted in less marginal bone resorption than threaded HA-coated and machined implants. The threaded HA-coated implants were found to have a higher survival rate than the threaded machined, 97.9% versus 95.2%, for both implants, which was a very good clinical outcome after 5 years.

Conclusions for bone response to CaP: micrometer level

CaP-coated implants usually demonstrate stronger bone responses than machined surfaces in experimental research. It is claimed in several studies that this difference is due to altered chemistry, but the result may equally well be dependent on the surface topography. Other studies present results not positively correlated with an increase in average height deviation; however, convincing evidence on whether the results depend on the chemical or topographical alteration is still lacking. If a coat is applied on a TPS surface it is often found to decrease the surface roughness. Coated surfaces are often very rough and perhaps some have passed the optimal roughness range. Unfortunately, many studies suffer from insufficient surface characterization, topographically as well as chemically, for the topographical versus chemical influence on bone response to be reliably separated.

Bone response to CaP: nanometer level

So far, there have been only a few publications on the *in vivo* response to CaP on a nanometer level. Mendes et al. [32] investigated the influence of CaP nanocrystals on the bone-bonding capability. Double-etched Ti and titanium alloy (Ti_6Al_4V) implants with and without coating were inserted in rats. The alloy implants demonstrated higher tensile forces than the c.p. Ti and the CaP-coated samples demonstrated higher tensile forces than the non-coated implants. SEM was the only method used to investigate the different surface topographies. Although the chemistry and topography may have contributed to the result, chemical investigations did not prove chemical bonding. The authors concluded that the nanometer structures had a positive effect on the bone-forming process. This was similar to the conclusion drawn by Meirelles et al. [33–35], who, in a series of studies, modified electro-polished cylinders and blasted screw-shaped implants with nanometer particles of CaP. The cylindrical implants were also coated with nanometer TiO_2 with the aim of separating the influence of nanometer structures from chemical influence. A rabbit model was used in the three above-cited papers and an enhanced bone formation was demonstrated for implants modified with nanometer particles; independent if those were CaP or TiO_2.

Li et al. [36] compared oxidized implants with and without nanometer CaP particles in a mini-pig model. SEM was the only method used to characterize the surface topography. After 8 weeks, an enhanced osseo-integration was found for the CaP-coated implants, although no statistical analysis was done. The hypothesis that a CaP coat on an etched titanium surface may enhance the bone-healing capacity was investigated by Schliephake et al. [37]. Both smooth-turned implants (Ra 0.1 μm) and etched implants (Ra 0.5 μm) were used as controls. Compared to the smooth-turned surface, the CaP-coated implants demonstrated a significantly improved bone formation around the implants. However, there were no differences between the etched and the coated implants, thus an additional positive effect from CaP could not be verified.

Conclusions for bone response to CaP: nanometer level

The few studies that exist indicate that nanometer structures have an impact on early bone healing. However, the optimal size and distribution of nanometer particles or pores applied on implant surfaces is still unknown, as is the case for micrometer roughness. Surface characterization has to be improved if nanometer research is to be successful.

Concluding remarks

In this article, we have discussed various types of surface manipulation of oral implants, with particular reference to the chemical–topographical influence of HA coatings. Although we are adamant in our conviction that controlled changes of surface roughness and surface chemistry may influence bone response, we remain unconvinced about the reasons behind reported stronger bone responses of different types of HA-coated implants. Is it mainly surface roughness or a chemical explanatory model that is relevant in the case of most published reports? In fact, so many different surface parameters may change when performing what seems to be one particular maneuver, such as applying a coat of HA with one or the other technique, and there seems to be no simple scientific explanation as to why bone responses are stronger. Naturally, we are aware of numerous *in vitro* studies suggesting, for instance, altered enzymatic responses to particular surface alterations, but these studies are by their very nature conducted in artificial environments, and cannot therefore be used as applicable evidence in the much more complicated *in vivo* situation with blood, hormonal, and loading influences, to mention just a few characteristics separating *in vitro* from *in vivo* studies. In fact, it is not uncommon for *in vitro* and *in vivo* approaches to present with dramatically different results. Physical changes of surface with increased surface energy further add to the confusion, since such changes may accidentally follow certain modes of implant manufacturing, such as fluoridization, which, if combined with UV light, has been demonstrated to increase surface hydrophilicity as well as potentially change the chemistry and nano-roughness of surfaces [38]. In another study by the same group of Japanese investigators [39], sintered titania coatings, in combination with UV light, were found to influence cells *in vitro*, but had an influence *in vivo* only at 2 weeks of follow-up, when there was an elevated bone response in a situation where controls, as well as test implants, had very small levels of bone, but displayed no difference between these surfaces at 4 weeks *in vitro*. The 2-week change observed may have depended on the elevated surface hydrophilia as well as on an increased nano-roughness. A recently introduced clinical implant allegedly demonstrates stronger bone responses to its high surface energy, but alternative modes of explanation may see this change as irrelevant and focus on the increased micro-roughness and/or increased nano-roughness of the same surfaces [11]. Taken together, the collected evidence points to an often dramatic change in bone response to different surface manipulations, but the individual importance of the several modes of surface changes introduced, deliberate or not, is commonly very difficult to interpret.

The present review has focused on one aspect of HA-coated implants, namely that they alter surface microtopography. However, the most common way of evaluating contributions to the bone response from HA-coated implants is by referring to their chemical effects. These alleged chemical effects are in no way contradicted by the present report, which only summarizes evidence of a surface topographical contribution that may work alone or in combination with a chemical effect. In fact, there is a third, if seldom quoted, reason for the effect of HA-coated implants, namely that of bone compression. This third theory is based on the fact that the great majority of applied HA coats in the literature are of a plasma-sprayed nature, i.e. minimally 50 μm thick. Hence, using a standardized size of defect for a control titanium implant and a HA-coated version of the same implant is potentially a benefit for the HA-coated implant, that of increased press-fit in the bone site due to this implant having minimally a 100 μm thicker body than its non-coated counterpart.

Originally, it was claimed that HA-coated implants mimicked bone and established some sort of direct chemical contact with bone – at one time termed bioactivity. However, this claim, even though interesting, is very difficult to prove conclusively. Attempts to compare qualitatively between the HA-coated and non-coated titanium implants on the one hand and bone tissue on the other, have failed to demonstrate any obvious differences. In fact, both HA-coated and Ti implants seem to give rise to dense contact with bone tissue at the ultrastructural level of resolution [40,41]. How then can the mechanisms of HA-coated implant anchorage be carefully analyzed? We see a need for new studies that carefully monitor factors such as surface chemistry, physics, and topography, since most of the current published data simply avoid this by assuming that the only matter of interest is surface chemistry. Until the publication of novel studies with adequate surface descriptions conducted with modern and appropriate techniques, we are limited to the following conclusion: in essence, effects of HA coatings may depend on altered chemistry, on altered surface topography, or on biomechanics (press-fit), or on a combination of these factors.

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