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Review

# Ion-substituted calcium phosphate coatings deposited by plasma-assisted techniques: A review

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ABSTRACT

One of the main critical aspects behind the failure or success of an implant resides in its ability to fast bond with the surrounding bone. To boost osseointegration, the ideal implant material should exhibit composition and structure similar to those of biological apatite. To this aim, the most common approach is to coat the implant surface with a coating of hydroxyapatite (HA), resembling the main component of mineralized tissues. However, bone apatite is a non-stoichiometric, multi-substituted poorly-crystalline apatite, containing significant amounts of foreign ions, with high biological relevance. Ion-substituted HAs can be deposited by so called "wet methods", which are however poorly reproducible and hardly industrially feasible; at the same time bioactive coatings realized by plasma assisted method, interesting for industrial applications, are generally made of stoichiometric (i.e. un-substituted) HA.

In this work, the literature concerning plasma-assisted deposition methods used to deposit ion-substituted HA was reviewed and the last advances in this field discussed. The ions taken into exam are those present in mineralized tissues and possibly having biological relevance. Notably, literature about this topic is scarce, especially relating to in vivo animal and clinical trials; further on, available studies evaluate the performance of substituted coatings from different points of view (mechanical properties, bone growth, coating dissolution, etc.) which hinders a proper evaluation of the real efficacy of ion-doped HA in promoting bone regeneration, compared to stoichiometric HA. Moreover, results obtained for plasma sprayed coatings (which is the only method currently employed for deposition at the industrial scale) were collected and compared to those of novel plasma-assisted techniques, that are expected to overcome its limitations. Data so far available on the topic were discussed to highlight advantages, limitations and possible perspectives of these procedures.



**Contents**



*Abbreviations:* HA, hydroxyapatite; CaP, calcium phosphate; OCP, octacalcium phosphate; TCP, tricalcium phosphate; CHA, carbonated hydroxyapatite; Mg-HA, magnesium doped hydroxyapatite; FA, fluorapatite; Sr-HA/CHA, strontium-doped hydroxyapatite/carbonated hydroxyapatite; Si-HA, silicon-doped hydroxyapatite; Mn-HA/CHA/OCP, magnesium-doped hydroxyapatite/carbonated hydroxyapatite/octacalcium phosphate; PS, plasma spray; MS, magnetron sputtering; RF-MS, radiofrequency magnetron sputtering; RAMS, right angle magnetron sputtering; MAPLE, matrix-assisted pulsed laser evaporation; PED, pulsed electron deposition.

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## 1. Introduction

### 1.1. Total joint replacement

Severe joint degeneration might occur as a consequence of trauma, pathological or degenerative diseases such as osteoarthritis and rheumatoid arthritis, to such an extent that total knee (TKR) and hip (THR) replacements alone reach every year >1 million cases in the USA and about 200,000 in the UK [1,2]. Future projections indicate that THR and TKR are expected to grow by 174% and 673%, respectively, by 2030 [3], corresponding to about 572,000 hip and 3.48 million knee interventions only in the USA [4,5]. However, revision rates for total joint replacement (TJR) procedures are still unacceptably high, 10 years survival rate being around 90% [6]. The number of revision interventions is expected to grow with the same rate as primary interventions [4,5]. Further, revision surgery is associated with higher occurrence of postoperative complications such as infections compared to primary interventions, as well as with more complex rehabilitation [7]. Indeed, implant infections occur for about 1–2% of primary interventions and up to 3–4% in case of revisions, leading, in the latter case, to the need for "re-revision procedures". Notably, patients with revisions are about 5–6 times more likely to undergo re-revision than in the case of primary intervention [8]. Together with the risks that derive from the need for retreatments, infections at both early or late stage have a strong economic impact [8–13]: considering primary interventions and revisions together, the sum of societal costs related to TJR treatments has been estimated to about 15 billion $ per year [6]. Due to the high social burden, it is of paramount importance to boost bone implant stability and decrease the number of revisions.

Cemented prostheses involve the use of polymethylmethacrylate (PMMA) to fill the gap between the implant and the surrounding bone [14,15]. However, the ability of self-curing PMMA bone cements to favor implant fixation is controversial, as a mismatch exists between its elastic modulus and that of bone, which prevents implant-bone bonding. Moreover, other drawbacks are generally highlighted, namely scarce bioresorbability, possible induction of necrosis in the surrounding tissue due to exothermic polymerization reactions during on-site curing and high susceptibility to wear, that arises because implant movement at the micro-scale results in the detachment of a significant amount of particles for polymeric materials [14].

Cementless prostheses, instead, rely on the ability of the implant to self-integrate in the surrounding bone [16]. The factors that determine the ability to create a stable bonding with the host tissue, hence the implant success, are the nature and the integrity of the bond that forms, and the quantity of bone around the implant that contributes to the implant fixation: early stabilization by direct bone/implant contact, instead of the formation of a fibrous tissue capsule, is a key parameter in determining long-term durability of the prosthesis.

Since metal-based implant are inert materials, thus lacking osteoconductivity and osteoinductivity, the common approach is to coat the implant with thick (30–300 μm) layers of hydroxyapatite (HA, $Ca_{10}(PO_4)_6(OH)_2$), which is generally believed to resemble the inorganic part of human and mammals' bones and teeth and thus to provide a suitable environment for bone bonding [15,17,18].

Clinical success of cementless prostheses depends upon initial fixation, that in turn depends on osseointegration achieved in the first few months after intervention, and on long term fixation. Osseointegration depends on a series of events (mesenchymal cell attachment, spreading, proliferation and differentiation into osteoblasts) that eventually lead to the formation of mineralized bone around the implant [16]. Lack of osseointegration is particularly harmful for patients with conditions that suppress bone formation, such as osteoporosis, diabetes, immunosuppressive therapy, smoking and also for patients that have undergone revision surgeries [16].

### 1.2. The biomimetic principle

According to the "biomimetic principle", a biomaterial engineered for bone replacement should be as similar as possible to the real bone, in terms of composition, crystallinity, lattice dimensions and Ca/P ratio, in order to elicit optimal biological behavior [19]. The inorganic phase of bone is normally referred to as hydroxyapatite; however biological apatite differs from pure HA in terms of composition, stoichiometry, crystallinity degree, crystal size/morphology and, as a direct consequence, ions availability in the biological medium [19,20]. Indeed, bone apatite is a carbonated-HA, containing significant amounts of foreign ions either incorporated into its lattice or adsorbed onto the crystal surface, characterized by a low crystallinity and a small crystals size [19]. Further, together with HA, other calcium phosphate phases, such as octacalcium phosphate (OCP), brushite (dicalcium phosphate di-hydrate, DCPD) and amorphous calcium phosphates (ACP) can be found in the human body [19].

Among the ions that are present in different concentrations in biomineralized tissues, some (namely carbonates, magnesium, fluorine,

**Table 1**
Amount of relevant ions in mammals mineralized tissues. All values are to be considered indicative (a, b [22], c [19]).

| | | Amount | | |
|---|---|---|---|---|
| | | Bone | Enamel | Dentine |
| $CO_3^{2-}$ | wt.% | 7.4a, b | 3.5a, b | 5.6a, b |
| Mg | wt.% | 0.72a, b | 0.44a, b | 1.23a, b |
| F | wt.% | 0.03a, b | 0.01a, b | 0.06a, b |
| Sr | wt.% | 0.05c | 0.03c | 0.04c |
| Na | wt.% | 0.9a, b | 0.5a, b | 0.6a, b |
| Cl | wt.% | 0.13a, b | 0.30a, b | 0.01a, b |
| K | wt.% | 0.03a, b | 0.08a, b | 0.05a, b |
| Si | ppm | 500c | | |
| Zn | ppm | | 263c | 173c |
| Mn | ppm | 0.17c | 0.6c | 0.6c |