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A novel method for local administration of strontium from implant surfaces

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Abstract This study proves that a film of Strontianite ($SrCO_3$) successfully can be formed on a bioactive surface of sodium titanate when exposed to a strontium acetate solution. This Strontianite film is believed to enable local release of strontium ions from implant surfaces and thus stimulate bone formation in vivo. Depending on the method, different types of films were achieved with different release rates of strontium ions, and the results points at the possibility to tailor the rate and amount of strontium that is to be released from the surface. Strontium has earlier been shown to be highly involved in the formation of new bone as it stimulates the replication of osteoblasts and decreases the activity of osteoclasts. The benefit of strontium has for example been proved in studies where the number of vertebral compression fractures in osteoporotic persons was drastically reduced in patients receiving therapeutical doses of strontium. Therefore, it is here suggested that the bone healing process around an implant may be improved if strontium is administered locally at the site of the implant. The films described in this paper were produced by a simple immersion process where alkali treated titanium was exposed to an aqueous solution containing strontium acetate. By heating the samples at different times during the process, different release rates of strontium ions were achieved when the samples were exposed to simulated body fluid. The strontium containing films also promoted precipitation of bone like apatite when exposed to a simulated body fluid.

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1 Introduction

The aim of the present study was to produce a novel implant surface for local administration of strontium ions (Sr^{2+}) that can improve the osseointegration of orthopedic and dental implants. Strontium has recently gained interest as it has been shown to be highly involved in bone remodeling where it not only affects bone formation positively and enhances osteoblast cell replication [1] but also reduces osteoclast activity [2]. The use of strontium ranelate in osteoporotic persons has proven to drastically reduce the number of vertebral fractures in the patients [3] as a result of the gain and improvement in bone geometry associated to the presence of strontium [4]. By local and targeted delivery of Sr^{2+} from the implant surface to the surrounding tissues, it is legitimate to assume that the bone healing process and implant fixation following surgery will be improved. The use of a non-degradable bioactive surface as carrier of Sr^{2+} is interesting as it ensures long-term in vivo stability and bioactivity of the surface. This is the reason for using a sodium titanate surface instead of a biodegradable coating of calcium phosphate (CaP) as carrier, which has been proposed by others [5–8].

Bioactive surfaces and coatings on titanium have been used for several years and offers superior anchorage of implants into bone [9–12]. The term "bioactivity" refers to the spontaneous nucleation and formation of apatite on the surface when the material comes in contact with body fluids [13]. The precipitated apatite coating resembles the mineral phase found in bone and acts like a bridging

between bone and implant as cells migrates to the apatite surface and integrates it with newly formed bone surrounding the implant [14]. Several materials, such as sintered hydroxyapatite [15] (HA), apatite–wollastonite [16] (A–W), crystalline TiO_2 [17], Bioglass® [18] and chemically treated titanium [19], possess this property and the clinical outcome of bioactive implants has proven superior to conventional implants [20–22]. The most thoroughly investigated and widely used method to transform the native and bioinert oxide of titanium into a bioactive surface was proposed by Kim et al. in 1996 [23]. They presented a method to produce a bioactive surface of sodium titanate by alkali- and a subsequent heat-treatment of a titanium substrate. This method constituted the starting point in this study where strontium was incorporated to a similar bioactive sodium titanate surface.

It has been shown that sodium titanate releases Na^+ via exchange with H_3O^+ molecules when immersed in aqueous salt solutions containing calcium and phosphate ions at physiological pH. This exchange creates Ti–OH groups on the surface that become partly deprotonated due to the slight difference between pH in the solution and the isoelectric point of the titanate titanium oxide [24]. The negative net charge of the surface attracts Ca^{2+} ions in the solution and an amorphous calcium titanate layer is formed at the surface [25]. Due to the similar characteristics between calcium and strontium (size and charge), it is here suggested that it is possible to incorporate strontium to sodium titanate in a similar manner to form a surface of strontium titanate. This substitution is believed to improve the biological response of the implant surface if Sr^{2+} ions are subsequently and slowly released into the surrounding tissues when implanted. The study presents two different methods based on this idea of substitution to incorporate Sr^{2+} to the surface of titanium substrates and describes the characteristics of these surfaces. The bioactivity of the strontium containing surfaces was tested in vitro by exposing the surfaces to a simulated body fluid (SBF) which is an acellular aqueous solution with ion concentrations similar to those found in human plasma [26]. This is a standard procedure where the formation of hydroxyapatite (HA) on the surface after days of immersion indicates the bioactivity of the surface [26]. HA ($Ca_{10}(PO_4)_6(OH)_2$) is an apatite that resembles the mineral phase found in bone, both in structure and composition [27].

2 Materials and methods

Titanium plates of grade 2 (2 × 2 cm) were mirror polished with 1200 SiC grit paper. The plates where ultrasonically cleaned with a neutral washing agent (Extran) in hot tap water for 5 min and rinsed in deionized water before ultrasonically cleaned in acetone for 5 min. After the cleaning, the plates where placed in a beaker containing a 5 M NaOH solution, the beaker were sealed with Parafilm® and placed in a heating cupboard set at 60°C for 24 h. After the alkali treatment, the plates were rinsed in deionized water and ethanol prior to blow-drying in N_2. The plates were then divided into two groups following the alkali treatment. The first group (*A*) was heat-treated at 600°C for 2 h while the other group (*B*) was left in a sealed plastic bag. Subsequently all plates were placed in individual plastic tubes containing 25 ml of 40 mM aqueous solution of strontium acetate ($Sr(CH_3COO)_2$, Sigma–Aldrich) in a heating cupboard set to 60°C for 4 days. After the strontium exposure, the plates where rinsed again in deionized water and ethanol before blow-dried in N_2. Now the second group of plates (*B*) was heat-treated at 600°C for 2 h before rinsed in deionized water and ethanol.

The plates were analyzed with Scanning Electron Microscopy (SEM, Leo 1550 equipped with an in-lens detector, Zeiss), gracing incident X-ray Diffraction (XRD, Diffractometer D5000, Siemens/Bruker), and X-ray Photoelectron Spectroscopy (XPS, PHI Quantum 2000, Physical Electronics) to investigate the composition and structure of the phases formed on the plates. After the examination of the surfaces, the plates were placed in individual plastic tubes containing 40 ml simulated body fluid (SBF) prepared according to Kokubo's recipe [26]. The tubes were placed in a heating cupboard set to 37°C for 1 week before analyzed with SEM, XRD and XPS again.

3 Results and discussion

XRD analysis proved the formation of crystalline $Na_2Ti_5O_{11}$ and Rutile TiO_2 on both samples (*A* and *B*). The XRD pattern of the surface after the alkali and subsequent heat-treatment of sample *A* (heat-treated before the strontium acetate exposure) can be seen in Fig. 1. Figure 2 displays the XRD pattern, and proves the formation of Strontianite ($SrCO_3$) on the surface, of sample *B* after immersion into the strontium acetate solution and the subsequent heat-treatment. The similarities between the formation of HA and Strontianite coatings on sodium titanate indicates that Sr^{2+} interacts with the surface in a similar way as Ca^{2+} and that Sr^{2+} can be incorporated in a titanate surface. The formation of Strontianite on sample *A* was proved in the same way. The morphology of the Strontianite coatings was examined with SEM. As seen in Fig. 3, the appearance of the surfaces differs between the two types of plates. Both surfaces proved to be porous, but the pore size was larger and the walls proved to be thinner and more delicate on the surface of sample *B*. XPS analysis

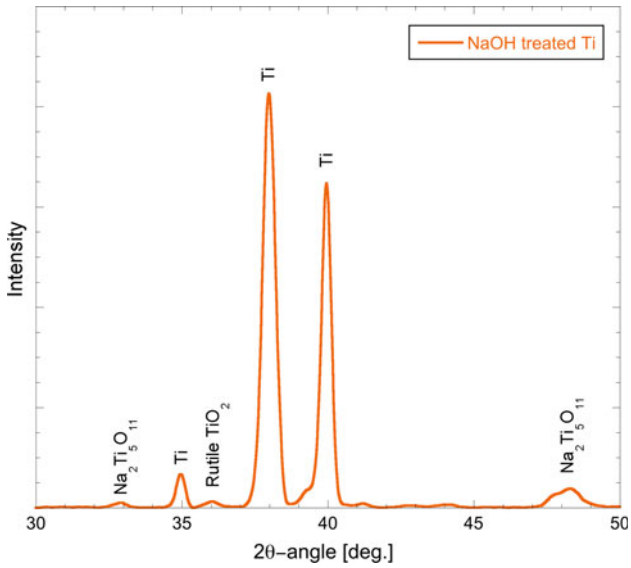

Fig. 1 XRD patterns of a titanium substrate exposed for a 5 M NaOH solution and subsequent heat-treatment, peaks in the pattern indicates the formation of Rutile TiO_2 and $Na_2Ti_5O_{11}$ on the surface

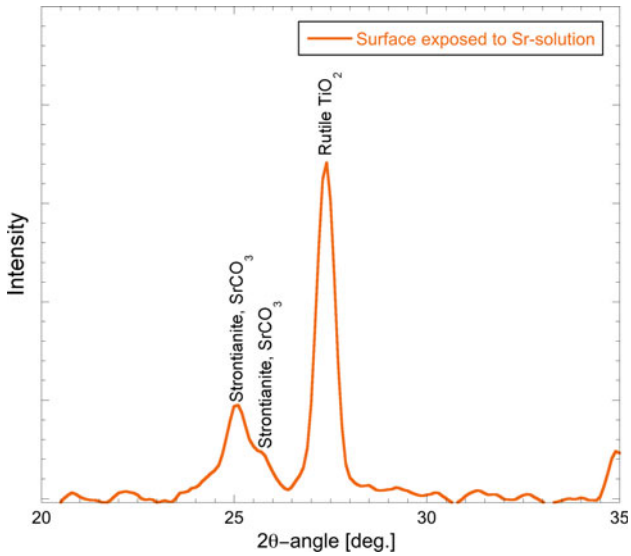

Fig. 2 XRD pattern of a sodium titanate surface exposed to a 40 mM strontium acetate solution, peaks in the pattern indicates the formation of Strontianite

revealed the presence of strontium in both surfaces and proved that the amount of strontium was higher in the surface of sample *B*. The Sr/Ti-ratio in the surface of sample *B* was 0.21 compared to 0.14 for sample *A*.

After immersion in SBF, a change in surface morphology of both sample *A* and *B* were seen with SEM (Figs. 3, 4) which proves a transformation or growth of the coatings on the samples. Both surfaces were porous but the coating on sample *B* consisted of needle like crystals whereas sample *A* had a more random crystal structure in the coating. Spherical crystal formations like the one found in Fig. 4b were found on both surfaces.

The newly formed coatings were not possible to analyze with XRD due to the limited thickness of the newly formed low-density coatings. No peaks in the XRD-patterns indicated any changes in the coatings on the surfaces.

XPS analysis proved that calcium and phosphate was present in both surfaces and titanium and strontium was still detectable. The Sr/Ti-ratio of sample *A* was 0.03 compared to 0.14 prior to the SBF immersion, which indicates a release of Sr^{2+} or dissolution of the Strontianite film during the formation of the new coating. Some strontium is believed to be present as substitute for calcium in the newly formed CaP-coating on the surface as the Ca/P-ratio in the coating was 1.38 but the (Ca + Sr)/P-ratio was found to be 1.64 which is consistent with the Ca/P-ratio of stoichiometric HA (1.67). On the other hand, in the second surface the Sr/Ti-ratio had only dropped from 0.21 to 0.19 suggesting that most of the strontium was still present in the surface. XPS data proved that the calcium content in this coating was very low with a Ca/P-ratio of 0.08, suggesting that a form of strontium phosphate coating with low calcium content had formed on the surface. This indicates a slower release rate of Sr^{2+} from this kind of surface, which enables the formation of a strontium phosphate (SrP) coating on the surface instead of a calcium rich structure. It is not clear if this SrP-coating will transform into a HA-like structure with time but it is not unlikely as this has been seen when a glass-cement system containing strontium was immersed into SBF [28].

It was clear that the strontium was more tightly bond to surface *B*, probably due to an increased stability of the heat-treated Strontianite coating and an incorporation of Sr^{2+} to the sodium titanate surface following the strontium exposure. This resulted in a more moderate release of Sr^{2+} to the SBF-solution but it also hindered an immediate formation of an HA-like structure on the surface.

The formation of a biologically similar apatite structure on surface *A* after immersion in SBF proved the concept of a strontium release from a bioactive surface on a titanium substrate. The formation of a strontium phosphate layer on surface *B*, which was heat-treated after the strontium exposure, pointed at a possible bioactivity of such a surface with a slow release of strontium.

Depending on the method, the release rate of strontium ions from the surface could be altered and the results points at the possibility to tailor the rate at which strontium is to be released from the surface.

For the first time, a way to produce a stabile bioactive surface with a strontium carbonate coating for local delivery of strontium ions was presented in the present study. This treatment/coating procedure is suggested to be employed on orthopedic and dental implants to improve the

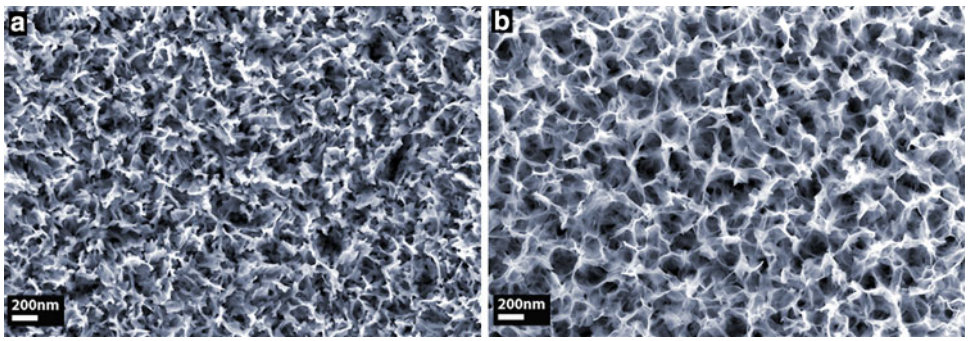

Fig. 3 SEM images of the sodium titanate surfaces **a** heat-treated prior to the strontium exposure and **b** heat-treated after the incorporation of strontium

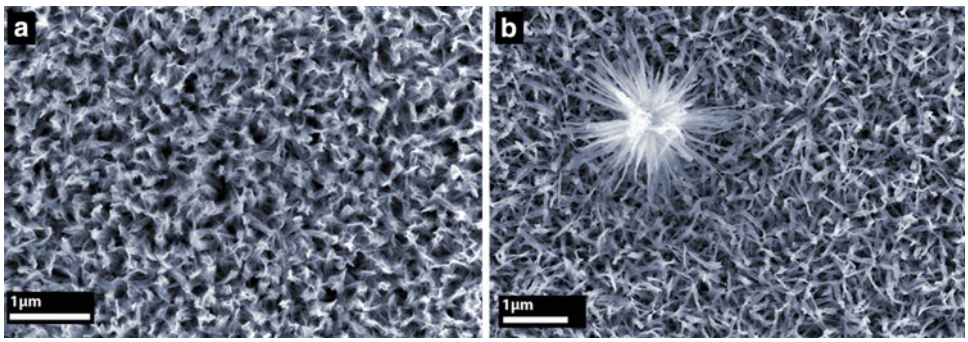

Fig. 4 SEM images of the sodium titanate surfaces after 7 days of immersion in SBF **a** sodium titanate heat-treated prior to the strontium exposure and **b** heat-treated after the incorporation of strontium

bone healing process following implantation and ensure long-term stability of the implant.

As a future outlook it would be very interesting to do further studies on the nature and adhesion of the Strontianite films and the bioactivity of the surfaces. By increasing the time for the in vitro bioactivity test and thereby letting the CaP coatings to grow thicker, it would be possible to analyze and study the bioactivity better. Also to do in vitro studies to investigate the cell response and finally investigate the biological response of the surfaces in an in vivo study is of great interest.

4 Conclusions

A new concept of local stimulation of bone formation at the site of an implant was presented in this study. The incorporation of strontium to the surface of chemically treated and bioactive titanium is believed to stimulate the regeneration of bone if it is released to the surrounding tissues. Two methods to incorporate strontium with different release rates were presented. Surfaces of sodium titanate were exposed to a strontium acetate solution which led to a formation of Strontianite ($SrCO_3$). A fast release of strontium from the surface was obtained if the sodium titanate surface was exposed to the strontium solution after a heat-treatment. This resulted in the formation of a strontium substituted apatite like structure on the surface when the substrate was exposed for SBF. A slow release of strontium from the surface was obtained when the sample was heat-treated after the strontium exposure, and resulted in the formation of a strontium phosphate structure on the surface when exposed to SBF.

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