

# Radio-opaque bioactive glass markers for radiostereometric analysis

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## Abstract

The objective of the study was to test the hypothesis that resorbable radio-opaque bioactive glass markers can be used in radiostereometric analysis (RSA). Cones made from (1) bioactive glass 1-06 with 2.5 wt.% BaSO<sub>4</sub>, (2) glass 1-06 with 10 wt.% BaSO<sub>4</sub>, (3) glass 1-06 without any additives and (4) nearly inert glass were created. The in vitro surface reactivity, as a surrogate of bioactivity, was analyzed using a simulated body fluid (SBF) immersion test. The in vivo performance was evaluated in the rat femur using biomechanical testing as well as histological and microcomputed tomography analysis of marker incorporation into bone. A phantom model RSA study using a porcine radius with a soft tissue envelope was carried out to determine the accuracy and precision of spherical markers for the measurement of fracture micromotion. SBF immersion studies and bone implantation studies showed that the addition of BaSO<sub>4</sub> slightly reduced surface reactivity in vitro and the bone-bonding properties of the bioactive glass in vivo. In the simulated RSA study with the selected resorbable marker composition (bioactive glass with 10 wt.% BaSO<sub>4</sub>), the accuracy of translation and rotation measurements in the longitudinal axis was  $\pm 51 \mu\text{m}$  and  $\pm 0.87^\circ$ , respectively. The precision of translation and rotation measurements in the longitudinal axis were  $9 \mu\text{m}$  and  $0.18^\circ$ , respectively. Bioactive glass markers with BaSO<sub>4</sub> additive appear to have adequate bone-bonding properties for marker stability and sufficient radio-opacity for RSA, but further preclinical comparison studies with tantalum markers are necessary.

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## 1. Introduction

Radiostereometric analysis (RSA) is considered the gold standard method for the quantitative assessment of in vivo micromotion of joint replacement and fracture fixation of implants [1,2]. It is also considered the most accurate and precise method for measuring polyethylene wear [3]. RSA is based on implantation of metallic landmarks (tantalum beads) into the body segments to be studied. Dual simultaneous radiographs are used in association with a calibration cage. The calibration cage contains a number of tantalum beads which are held in fixed, well-defined posi-

tions enabling the construction of a three-dimensional coordinate system. The body part to be studied is either placed inside or in front of the calibration cage depending on its size. A pair of radiographs is then used to determine the location of the markers three-dimensionally, and this allows the calculation of relative displacements between different segments using special software. The RSA method enables highly accurate measurement of both translation and rotation in three dimensions [2]. A drawback of the method is that tantalum markers have to be attached to the implants or bone fragments being studied. Advancements in computer programs and digital radiography have enabled model-based techniques to be developed [4]. These techniques are based on using the three-dimensional properties of the implant rather than on the use of attached markers [4]. The accuracy of model-based RSA has been

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shown to be similar to marker-based RSA [4]. The presently available model-based RSA techniques do not, however, eliminate the need to mark bone fragments [1].

The tantalum markers used in RSA studies have an excellent radiographic opacity but are permanently deposited in bone. Tantalum markers have been used in clinical trials for 25 years in more than 5000 patients without adverse effects [1,5], although permanent markers may not be necessary. A possible alternative is the use of a resorbable biomaterial. The ability of silica-based bioactive glasses to chemically bond with bone could provide an additional advantage of good marker stability when anchored in bone. The main shortcoming of bioactive glasses is that they have radio-opacity similar to that of cortical bone [6]. One option is to add a radio-opaque additive. Barium sulphate ( $\text{BaSO}_4$ ) is frequently used as an opacifier in bone cements [7]. In this study  $\text{BaSO}_4$  was used as an opacifier in the creation of spherical radio-opaque bioactive glass RSA markers. The objective of the study was to test the hypothesis that resorbable radio-opaque bioactive glass markers can be used in RSA.

## 2. Materials and methods

### 2.1. Preparation of bioactive glass implants

The composition of the selected bioactive glass (coded 1-06, Åbo Akademi University, Turku, Finland) was 50.0 wt.%  $\text{SiO}_2$ , 4.0 wt.%  $\text{P}_2\text{O}_5$ , 0.2 wt.%  $\text{B}_2\text{O}_3$ , 5.9 wt.%  $\text{Na}_2\text{O}$ , 12.0 wt.%  $\text{K}_2\text{O}$ , 22.6 wt.%  $\text{CaO}$ , 5.3 wt.%  $\text{MgO}$  [8]. This glass composition was chosen since it is known to have good bioactivity as well as a wide working range, enabling manufacture of various morphologies [8]. Native glass 1-06 is poorly visible on plain X-rays. Two radio-opaque glasses were produced by adding  $\text{BaSO}_4$  to the basic glass composition.

This study compared the following four glasses: (1) bioactive glass 1-06 with 2.5 wt.%  $\text{BaSO}_4$ , (2) bioactive glass 1-06 with 10 wt.%  $\text{BaSO}_4$ , (3) bioactive glass 1-06 without any additives and (4) nearly inert glass (flat glass). In this study these four glasses were coded as glass 1-06, 1-06B2.5, 1-06B10 and FG, respectively.

Glass cones (truncated) with height 7 mm, base diameter 3 mm, tip diameter 1.9 mm and a tip angle of  $9^\circ$  were manufactured for in vitro and in vivo studies. As a first step to

produce bioactive glass 1-06, Ph.Eur analytical reagent grade of  $\text{CaCO}_3$ ,  $\text{Na}_2\text{CO}_3$ ,  $\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$ ,  $\text{H}_3\text{BO}_3$ ,  $\text{K}_2\text{CO}_3$ ,  $\text{MgO}$  as well as commercial quartz sand (Belgian Sand 99.8% purity) were mixed and used for the glass batches (Table 1). These batches (giving 300 g of glass) were melted in a platinum crucible for 3 h at  $1360^\circ\text{C}$  in an electrical laboratory furnace. The melt was first cast into a plate using a pre-heated graphite mould, annealed at  $520^\circ\text{C}$  for 1 h, allowed to cool to room temperature in an annealing furnace and crushed. In the next manufacturing step the crush was either used as such to produce generic glass 1-06, or mixed with 2.5 and 10 wt.% of Ph.Eur analytical reagent grade  $\text{BaSO}_4$  to produce the two novel radio-opaque glasses. The crush was re-melted at  $1360^\circ\text{C}$  for 3 h, and, to produce conically shaped implants, the melts were cast into pre-heated graphite moulds, annealed at  $520^\circ\text{C}$  for 1 h, and allowed to cool to room temperature in an annealing furnace. In this way all the glasses used in the study were subjected to the same melting and annealing procedure. Furthermore, only one melting might not be enough to ensure a homogeneous glass. Oxide compositions of the glasses used in the study were determined by energy dispersive X-ray analysis (EDXA) (Table 2).

### 2.2. In vitro characterization of implants

The bioactive glass undergoes a cascade of sequential stages of surface reactions during in vivo implantation and the formation of a carbonated hydroxyapatite layer leads to chemical bonding with hydroxyapatite of the growing new bone. In vitro, bioactive glass implants also form silica-rich and apatite layers, and this activity results in changes of the ionic concentrations in simulated body fluid (SBF) [9,10].

The surfaces of implants were first examined by X-ray diffraction (XRD, Philips PW-series) for possible structural changes such as crystallization of the glass due to the addition of  $\text{BaSO}_4$ . Specimens of three bioactive glass compositions were immersed in SBF. The specimens had the same morphology as the implants. The ratio of the surface area of the materials to the volume of the SBF (SA/V ratio) was  $0.4\text{ cm}^{-1}$ . The concentrations of soluble calcium (Ca), phosphorus (P) and silicon (Si) were monitored at 4, 8, 24, 96 and 168 h. For each of the bioactive glass compositions, three parallel specimens were immersed in SBF and

Table 1  
Raw materials used to prepare the glasses used in the study.

Product name	Provider	Lot number	Assay (%)
Calcium carbonate $\text{CaCO}_3$	Yliopiston apteekki, Analyttinen laboratorio, Finland	62,607	98.7
Sodium carbonate $\text{Na}_2\text{CO}_3$	Sigma–Aldrich Co.	6224A	100.0
Calcium phosphate dibasic dehydrate $\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$	Sigma–Aldrich Co.	51440	100.4
Boric acid $\text{H}_3\text{BO}_3$	Merck KGaA	A696960 603	100.0
Potassium carbonate $\text{K}_2\text{CO}_3$	Sigma–Aldrich Co.	51,820	99.6
Magnesium oxide $\text{MgO}$	Yliopiston apteekki, Analyttinen laboratorio, Finland	62,283	99.4
Barium sulphate $\text{BaSO}_4$	Sigma–Aldrich Co.	04512AD	99
Belgian sand Mam1	SRC–Sibelco NV		99.8

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