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Biodegradable Fe-based alloys for use in osteosynthesis: Outcome of an in vivo study after 52 weeks

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ABSTRACT

This study investigates the degradation performance of three Fe-based materials in a growing rat skeleton over a period of 1 year. Pins of pure Fe and two Fe-based alloys (Fe–10Mn–1Pd and Fe–21Mn–0.7C–1Pd, in wt.%) were implanted transcortically into the femur of 38 Sprague–Dawley rats and inspected after 4, 12, 24 and 52 weeks. The assessment was performed by ex vivo microfocus computed tomography, weight-loss determination, surface analysis of the explanted pins and histological examination. The materials investigated showed signs of degradation; however, the degradation proceeded rather slowly and no significant differences between the materials were detected. We discuss these unexpected findings on the basis of fundamental considerations regarding iron corrosion. Dense layers of degradation products were formed on the implants' surfaces, and act as barriers against oxygen transport. For the degradation of iron, however, the presence of oxygen is an indispensable prerequisite. Its availability is generally a critical factor in bony tissue and rather limited there, i.e. in the vicinity of our implants. Because of the relatively slow degradation of both pure Fe and the Fe-based alloys, their suitability for bulk temporary implants such as those in osteosynthesis applications appears questionable.

1. Introduction

Biodegradable metals have been a subject of extensive research in recent years, and there is ongoing interest in these materials, not least because of their increasing number of potential applications [1–3]. Biodegradable materials are not only highly interesting for osteosynthesis and coronary devices, but also for degradable wound closing devices [4], tracheal stents [5] and the treatment of aneurisms [6]. Their potential is ascribed to the expectation that a degradable material will reduce the long-term risks and side effects, such as chronic inflammation, in-stent restenosis or inability to adapt to growing tissue, which are normally associated with permanent implants. Moreover, in the case of osteosynthesis, in particular, degradable implants require only one surgical intervention and circumvent the need for implant removal. They therefore contribute to patient comfort and help to reduce medical costs.

In this context, biodegradable Fe alloys are interesting candidates for such applications. The suitability of iron as a degradable implant material has been verified in preliminary in vivo studies, in which stents fabricated from pure iron were investigated in animal models [7–10]. The most important results were that no local or systemic toxicity, no early restenosis due to thrombotic processes, and no pronounced inflammation reactions were observed. The neointimal proliferation was found to be comparable with that of standard materials such as Co–Cr alloys and stainless steel 316L. However, the stents remained relatively intact up to 1 year after their placement, implying that their in vivo degradation rate was too low, and the material's performance approached that of permanent implants. Moreover, the mechanical properties of pure iron are limited and not well suited for implant materials. Consequently, a material that shows faster in vivo degradation and better mechanical properties needs to be found.

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This study therefore concentrated on the development of biodegradable Fe alloys with increased degradation rate, appropriate mechanical performance and simultaneous good biocompatibility. Hermawan et al. [1] presented Fe–Mn alloys with mechanical properties similar to those of stainless steel 316L and higher in vitro degradation rates. However, the degradation rate of the Fe–Mn alloys is still one order of magnitude lower than that of magnesium alloys (which represent a second class of engineering materials for degradable implants) and may still be too low for practical applications. To further extend freedom in alloy design and to achieve even higher degradation rates, a design strategy for Fe-based alloys has already been presented [11]. The Fe–Mn–Pd alloys produced according to this approach feature excellent mechanical properties, especially high strength (Table 1), and a degradation rate in in vitro experiments that is higher than those of pure Fe and Fe–Mn alloys [11]. The high strength values of these alloys, in particular, enable the realization of slender and filigree implant designs that are favorable for two reasons: first, they introduce less material into the body to degrade; and second, their degradation kinetic—slower than that of Mg alloys—becomes tolerable because of the smaller implant dimensions.

While the in vitro degradation rate of the Fe–Mn–Pd alloys exceeds that of pure Fe and Fe–Mn alloys, the in vivo degradation of these materials has not so far been investigated. Moreover, the degradation rate of pure Fe implants was not determined in the course of previous studies. Consequently, the present study aimed to assess the in vivo degradation of pure Fe and the newly developed Fe alloys. It used a rat model, where pins were transcortically implanted into the femur and monitored over a period of 1 year. Degradation was studied by weighing explanted specimens and was complemented by determining volume loss based on microfocus computed tomography (μ-CT) data. Surface analysis and histological sections were also performed on the explanted samples.

2. Materials and method

2.1. Implants

In this study, three different materials were investigated (alloying content in wt.%): pure Fe (ferromagnetic, Armco quality); Fe–10Mn–1Pd (ferromagnetic); and Fe–21Mn–0.7C–1Pd (paramagnetic). Details concerning production and characterization in terms of microstructure and mechanical performance for Fe–10Mn–1Pd are given in Ref. [12] and for Fe–21Mn–0.7C–1Pd in Ref. [13]. The final heat treatment of the alloys investigated here involved aging of Fe–10Mn–1Pd for 30 h at 500 °C, and aging of Fe–21Mn–0.7C–1Pd for 10 min at 700 °C. The material had already been tested in vitro for biocorrosion, blood compatibility and cell viability [11,14,15]. The implants used for the present in vivo studies were cylindrical pins of diameter 1.6 mm and length 8 mm. After machining, these pins were cleaned with pure ethanol in an ultrasonic bath and dried in warm air. Before operation, they were weighed, and their pin volume and surface were determined via high-resolution μCT scans over a period of 52 weeks. Preoperatively, all pins were sterilized by gamma radiation.

Table 1
Strength values of pure Fe and different Fe-based alloys.

Alloy	YS (MPa)	UTS (MPa)	References
Fe (Armco)	230 ± 5	300 ± 5	[13]
316L	290 ± 15	630 ± 5	[13]
Fe–25Mn	361 ± 33	723 ± 19	[28]
Fe–35Mn	234 ± 7	428 ± 7	[28]
Fe–10Mn–1Pd	1076 ± 6	1198 ± 42	[29]
Fe–21Mn–0.7C–1Pd	1095 ± 35	1320 ± 15	[13]

YS, yield strength; UTS, ultimate tensile strength.

2.2. Experimental design

Rats were housed in groups of four in clear plastic cages on standard bedding. Water and a standard pellet diet were given ad libitum. The Austrian Ministry of Science and Research authorized the animal experiments (accreditation number BMWF-66.010/0087-II/3b/2011), which were all conducted under animal ethical conditions.

Thirty-eight 5 week old male Sprague–Dawley rats with body weights of 140–160 g were used in this study. Of these, 36 underwent μCT scans, and two were subject to histological examinations.

To check the correct pin position, a μCT investigation was performed within 1 week after operation. At four prearranged time points (4 weeks, 12 weeks, 24 weeks and 52 weeks after pin implantation), ex vivo high-resolution μCT scans were also performed. For this purpose, the 36 rats intended for the μCT scans were separated randomly into three groups ($n = 12$ each). Under general anesthesia, each rat had two identical pins of the same alloy implanted into its distal femoral bones. Thus there were three rats (six femoral bones) per alloy group ($n = 3$) and time point post implantation ($n = 4$) for the radiological assessment.

Two 5 week old rats were used for histological investigations. Histological slices were investigated at the 36th week and limited to pure Fe pins.

2.3. Surgical procedure and postoperative treatment

Under general anesthesia, the pins were implanted into the femoral mid-diaphyseal region of the rats, as reported in a previous study [16]. Perioperative pain treatment was also identical to that reported in a previous study [16]. After surgery, the rats were allowed to move freely in their cages without external support and with their weight bearing unrestricted. Clinical observation was performed daily throughout the study period.

2.4. Euthanasia

Volatile isoflurane (Forane®, Abbot AG, Baar, Switzerland) was used for general anesthesia. Subsequently, 25 mg sodium thiopental (Thiopental® Sandoz, Sandoz GmbH, Kundl, Austria) was injected into the cardiac ventricle, causing direct cardiac arrest. Immediately after harvest of the femur, all soft tissues were carefully removed. The bone implant specimen of each alloy was embedded in dry ice, and the μCT scan was performed.

2.5. Preparation of the bone-pin model

Immediately after euthanasia, a longitudinal skin incision was made medially at each rat's femur. After transection of the muscles, the femur bone was carefully exposed and ex-articulated at the adjacent joints. The area beneath the implant was untouched and was covered by thin laminas of remaining tissue in order not to change the existing pin-bone conditions. Immediately after total preparation, the bone was wrapped in physiological saline-solution-dipped swab material and brought to μCT.

2.6. High-resolution μCT and image reconstruction

To determine the pin volume and the pin surface, μCT images were assessed using a Siemens Inveon™ Research Workplace "Acquisition 1.2.2.2". The μCT scans were conducted using a polychromatic source at 80 kV voltage, 500 μA current with an