

RESEARCH ARTICLE

Exploring the biodegradability of candidate metallic intravascular stent materials using X-ray microfocus computed tomography: An in vitro study

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Abstract

In vitro testing for evaluating degradation mode and rate of candidate biodegradable metals to be used as intravascular stents is crucial before going to in vivo animal models. In this study, we show that X-ray microfocus computed tomography (microCT) presents a key added value to visualize degradation mode and to evaluate degradation rate and material surface properties in 3D and at high resolution of large regions of interest. The in vitro degradation behavior of three candidate biodegradable stent materials was evaluated: pure iron (Fe), pure zinc (Zn), and a quinary Zn alloy (Zn–Ag–Cu–Mn–Zr). These metals were compared to a reference biostable cobalt–chromium (Co–Cr) alloy. To compare the degradation mode and degradation rate evaluated with microCT, scanning electron microscopy (SEM) and inductively-coupled plasma (ICP) were included. We confirmed that Fe degrades very slowly but with desirable uniform surface corrosion. Zn degrades faster but exhibits localized deep pitting corrosion. The Zn alloy degrades at a similar rate as the pure Zn, but more homogeneously. However, the formation of deep internal dendrites was observed. Our study provides a detailed microCT-based comparison of essential surface and corrosion properties, with a structural characterization of the corrosion behavior, of different candidate stent materials in 3D in a non-destructive way.

KEYWORDS

biodegradable stent, high-resolution microCT, in vitro static immersion testing, metallic alloy, surface properties

1 | INTRODUCTION

Cardiovascular diseases (CVDs) are the leading cause of death globally. Atherosclerosis is the primary cause of coronary heart disease, ischemic stroke, and peripheral artery diseases¹ and causes narrowing and possibly obstruction of the arteries. Aortic aneurysm or the widening of the aorta due to a weakness in the vessel wall, leads to death in 65% of patients.² The gold standard treatment for both narrowed arteries and aortic aneurysm is vascular stenting. Until recently, stent technology was based on permanent stents. Cobalt–chromium (Co–Cr) is one of the standard materials used for permanent metallic frameworks.³ However, permanent stents are associated with long-term complications due to late-stage thrombosis, stent strut fracture, chronic inflammation, and in-stent restenosis.^{4,5} During the last two decades, biodegradable polymers and metals have been studied in an effort to replace permanent stents.^{6,7} A stent is required to last for 6–12 months during arterial remodeling and healing to provide mechanical support, and after that, the presence of the stent within the blood vessel is not necessary anymore.⁸ Polymer-based bioresorbable scaffolds have been investigated, but their poor mechanical properties (low ultimate tensile strength), inability to expand completely with balloon dilatation, their higher delayed thrombogenicity, and the fact that they are not radiopaque have shifted focus to their metallic counterparts.^{5,6}

Iron (Fe) and magnesium (Mg) alloys have been reported to be suitable materials for biodegradable stents owing to their good biocompatibility and mechanical properties.^{9–16} However, Mg alloys have a degradation rate that is too high, which is also associated with the evolution of hydrogen gas (H₂). The latter is a big concern due to the release of H₂ bubbles, which may block the blood stream.^{17,18} Fe has a reasonable degradation rate (although considered too slow for a biodegradable stent) and appropriate mechanical properties, but some concerns have been raised related to the stability of the corrosion product.⁶ A third class of metallic alloys based on zinc (Zn) has been introduced in 2013, and it appears to have an appropriate degradation rate and good biocompatibility.^{6,19} However, pure Zn still lacks of mechanical strength and undergoes strain softening,⁴ thus requiring adequate alloying.²⁰ As a result, the optimal alloy with suitable mechanical properties, proper corrosion rate and behavior, and appropriate biocompatibility still needs to be found. Attempts at alloying pure Zn have been undertaken.^{4,20,21} However, the addition of elements and their varied concentrations can have strong effects on corrosion and biocompatibility characteristics.

In vitro corrosion test methods are a first screening step to determine if a material is potentially appropriate to be used for biodegradable stents and to learn about the effects of metallurgical modifications on corrosion properties. They do not require complicated surgeries and sacrificing animals and some methods are well accepted to evaluate the degradation rate and surface properties of candidate alloys. To determine the corrosion rate, currently used techniques include mass loss measurements, pH monitoring, potentiodynamic polarization, electrochemical impedance spectroscopy,

and released ion concentration evaluation using inductively-coupled plasma (ICP).²² However, these techniques often do not provide information on degradation mechanisms (mass loss), require pH change which is normally avoided for in vitro tests (pH monitoring), are destructive to the surface (potentiodynamic polarization), or only provide overall corrosion behavior information as opposed to local information (mass loss, pH monitoring, potentiodynamic polarization, ICP).²² Beyond the corrosion rate, the surface properties of candidate stent materials are important because they are a determinant of thrombogenicity and tissue reaction, that is, the nature of the metal surface is crucial to blood compatibility. A stent needs to have an athrombogenic surface to enhance biocompatibility. A smooth surface can help prevent the activation and aggregation of platelets, which is recognized as a part of the thrombosis process.²³ Previous studies with animal models have shown that metallic surface treatment using electrochemical polishing decreased not only thrombogenicity but also neointimal hyperplasia.²⁴ Surface properties can be determined at high resolution (up to the nm-scale) for small regions of interest with techniques such as scanning electron microscopy (SEM), scanning probe microscopy, and profilometry for small surface areas.²⁵

Our aim was to perform a detailed evaluation of the degradation behavior and surface roughness properties of four different metals: a Co–Cr alloy (biostable reference), pure Fe, pure Zn, and a Zn–Ag–Cu–Mn–Zr alloy. The quinary Zn alloy is an advanced and newly developed alloy that has improved mechanical properties compared to pure Zn and was shown to have inflammation-resistant properties compared to other Zn alloys.²⁰ X-ray microfocus computed tomography (microCT) has been used in the past to visualize corrosion products and to evaluate the in vitro and in vivo degradation rate of different metals using the volume loss method. However, this has been done at low resolution (from 6 μm and up to several tens of μm voxel size).^{26–31} We have used high-resolution microCT imaging (1 μm voxel size) for improved accuracy of the corrosion rate measurements and have registered the volume of the wires before and after degradation. Then, we further optimized microCT-based post-processing tools to study not only the degradation rate, but also the surface properties of the different metals, by improving an in-house developed Matlab routine that detects the surface profile and allows to compute the roughness parameters of both straight and curved surfaces. The surface properties provided information about the roughness but also offered valuable insights into the corrosion behavior, distinguishing between homogeneous and heterogeneous corrosion patterns by investigating the peaks and valleys, and the total and average roughness of the surface profile. Wires were used to mimic a single stent strut, as a simplified and low-cost alternative to full stents.³² 3D microCT images were acquired prior to and after in vitro immersion tests at three different time points (1, 4, and 7 days). The microCT images allowed to obtain a detailed comparison of the degradation rate through the volume loss method, the changes in surface roughness over time, as well as the degradation behavior of the different metals. Results obtained with the volume loss method were validated by measuring

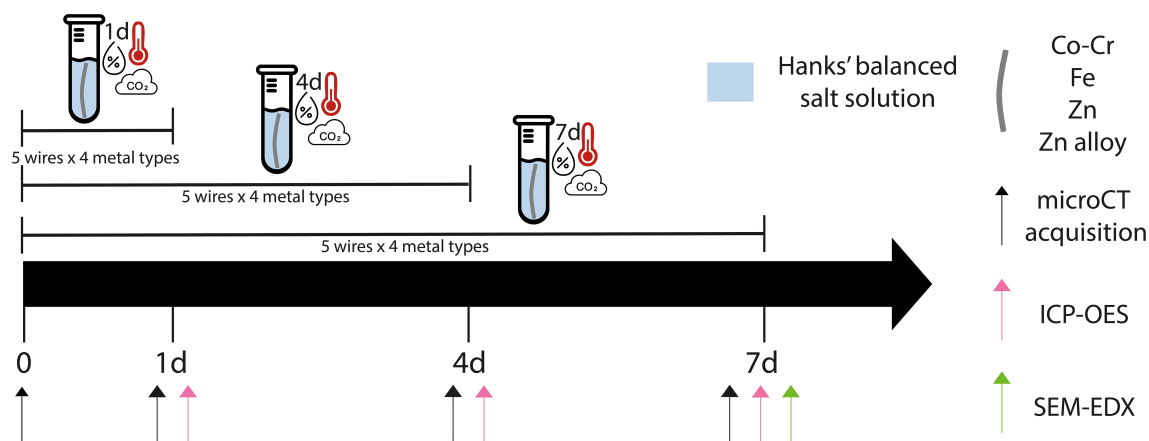


FIGURE 1 Timeline for experiments. Co—Cr, Fe, Zn, and Zn alloy wires were immersed in Hanks' balanced salt solution at physiological conditions (37°C and 5 vol.% CO₂) for 1, 4, or 7 days (5 wires × 4 metal types × 3 time points). MicroCT acquisition of the wires was performed at 0, 1, 4, and 7 days ($n = 5$). Inductively-coupled plasma – optical emission spectrometry (ICP-OES) was performed at 1, 4, and 7 days ($n = 5$). Scanning electron microscopy – energy dispersive X-ray spectroscopy (SEM-EDX) was performed at 7 days ($n = 1$).

the released ion concentration through ICP. The degradation behavior observed in the microCT images was compared with SEM. SEM was also combined with energy dispersive X-ray spectroscopy (EDX) to identify the nature of the corrosion products. The combination of these techniques for the same samples was possible thanks to the non-destructive character of microCT. This study gives initial insights into the degradation behavior of different metals, providing essential information before going to in vivo studies in animals.

2 | MATERIALS AND METHODS

2.1 | Samples

Four types of wires were purchased. The cobalt-chromium alloy (40Co–20Cr–15Fe–15Ni–7Mo–2Mn–C–Be (wt %)) wire of diameter 0.25 mm (ref. CO125140), the high purity iron (Fe 99.99 + wt %) wire of diameter 0.25 mm (ref. FE005141), and the high purity zinc (Zn 99.99 + wt %) wire of diameter 0.25 mm (ref. ZN00-WR-000115) were purchased at GoodFellow Corporation (Oakdale, PA, USA). The quinary zinc alloy (Zn–4Ag–0.8Cu–0.6Mn–0.15Zr (wt %)) was developed by Dr. Jaroslav W. Drelich.²⁰ The quinary zinc alloy wire of diameter 0.25 mm was produced by Fort Wayne Metals (Fort Wayne, IN, USA). Figure 1 illustrates the experimental steps.

2.2 | In vitro static immersion

Fifteen 20 mm-long wires of each metal or metallic alloy were cut, washed with Milli-Q water and dried with compressed air. They were washed again with ethanol. The immersion tests were done in a Hanks' balanced salt solution. They were carried out according to the ASTM G31-72 standard.³³ The solution was prepared with 9.5 g of balanced Hanks' salts (H1387, Sigma-Aldrich) and 0.35 g of NaHCO₃

TABLE 1 Ionic concentrations determined for each metal type using ICP-OES.

Metal type	Elements for which concentration was detected
Co—Cr alloy	Co, Cr
Pure Fe	Fe
Pure Zn	Zn
Quinary Zn alloy	Zn, Ag, Cu, Mn, Zr

in 0.85 L of distilled water. Using a pH meter (WTW pH 330), the pH of the solution was adjusted to 7.4 by the addition of HCl 1 M or NaOH 1 M. Distilled water was then added to reach 1 L of solution. Before immersing each wire in the solution, the pH was once again measured to verify its stability. Containers were stored statically in an incubator (Binder CB 170) at 37°C and 5 vol.% CO₂. Each container was filled with 33 mL of Hanks' solution (according to the standard). The upper part of each wire was attached to the container cap with a piece of sewing thread to suspend the wire in the solution. Incubation times were 1, 4, or 7 days. The solution was replaced after 48 h for the longer time points to maintain constant pH throughout the duration of incubation. After incubation, wires were rinsed with distilled water and ethanol to remove non-adherent corrosion precipitates on the surface. Both the remaining Hanks' solution and the rinsing liquid were kept. $N = 5$ per time point and per metal type.

2.3 | Inductively-coupled plasma – optical emission spectrometry

Inductively-coupled plasma – optical emission spectrometry (ICP-OES) (Agilent Technologies 5100) was performed to determine the ion concentration in the Hanks' solution and rinsing liquid after wire immersion. Concentrations of the different elements were measured in mg L^{−1}. The

detection limit of the ICP-OES system was 0.05 mg L^{-1} for Ag and Cr and 0.01 mg L^{-1} for the other elements. The elements for which the concentration has been determined are listed in Table 1 for each metal type.

2.3.1 | Corrosion rate based on ICP-OES

The corrosion rate was determined using the ion-release concentration:

$$CR = \frac{cV}{\rho At}$$

CR is the corrosion rate ($\text{mm}\cdot\text{year}^{-1}$ or mmpy), ρ is the metal density ($\text{mg}\cdot\text{mm}^{-3}$), c is the released ion concentration ($\text{mg}\cdot\text{L}^{-1}$), V is the initial solution volume (L), A is the exposed surface area (mm^2), and t is the exposure time (years).

2.4 | High-resolution microCT acquisition

The lower 2 mm of each wire was imaged with microCT (Phoenix NanoTom M, GE Measurement and Control Solutions, Germany) prior to (time point 0) and after immersion. The NanoTom M is equipped with a 180 kV/15 W energy micro/nanofocus X-ray tube and a diamond-coated tungsten target was used for all acquisitions. Images were acquired at a $1 \mu\text{m}$ isotropic voxel size, with a source voltage of 100 kV and a tube current of $42 \mu\text{A}$. The exposure time was 500 ms. Imaging was done in mode 0, 2400 projections were acquired with averaging 1 and skip 0. All acquisitions took 20 min in fast scan mode. A copper filter of 0.1 mm thickness was placed between the source and the sample. The microCT datasets were reconstructed with the Datos|x software (GE Measurement and Control Solutions). A beam hardening correction (BHC) of 6 was applied. BHC goes on a scale from 0 (no correction applied) to 10 (very strong correction applied). Three different post-processing filters were applied in the reconstruction software: inline median (projections are filtered during reconstruction using a 3×3 median filter which reduces the noise in the volume), ROI-CT filter (increases the resolution of the CT dataset for a selected ROI of the object), and filter volume (volume is filtered in slices after reconstruction using the Unsharp Masking Filter, enhancing object edges). Slices were exported as 16-bit XY slices (.tiff) and then converted to 8-bit (.bmp) images, while simultaneously adapting the grayscale histograms of the datasets to normalize them to each other using an in-house developed Matlab routine.³⁴

2.5 | Surface roughness analysis based on microCT

Two longitudinal cross-sections (YZ and XZ slices) of each acquired microCT dataset of the wires after immersion were exported using Dataviewer (Bruker MicroCT, Kontich, Belgium). The same was repeated for three microCT datasets of each type of wire before immersion (time point 0). Using an in-house developed Matlab routine described in³⁵ and

extended here for non-straight surfaces (Figure 2), the 2D surface roughness was determined for each section on both edges of the wire cross-sections (resulting in 4 surface profile lines per wire). The following roughness parameters were determined: R_a (average roughness (μm) over the evaluated length), R_t (total roughness (μm), the vertical distance between the lowest and highest points over the evaluated length), and R_{ku} (Kurtosis or a measure of the sharpness of the roughness profile, $R_{ku} < 3$ for a bumpy surface and $R_{ku} > 3$ for a spiky surface).

2.6 | Corrosion behavior based on microCT

The profile lines of each wire used for the surface roughness analysis were used to determine the corrosion behavior: homogeneous versus heterogeneous and pitting versus surface corrosion, only after the 4 day-time point, at which most variation is observed between metal types. This was done by computing the mean of peaks (μm), mean of valleys (μm), standard deviation (μm) of peaks, and standard deviation (μm) of valleys for the surface profile lines of each wire (4 profiles per wire).

2.7 | Scanning electron microscopy – energy dispersive X-ray spectroscopy (SEM–EDX)

SEM (Ultra 55 FEG SEM, Zeiss, Germany) was performed on the 7-day samples to confirm the degradation behavior observed in the microCT images. Images of the surface of the wires were obtained with a voltage of 30 kV ($N = 1$ per material). Other wires of the same time point were embedded in epoxy resin and polished to $1 \mu\text{m}$ grain size for obtaining cross-sectional images with a voltage of 15 kV ($N = 1$ per material). EDX (Bruker QUANTAX, Germany) was performed on the latter to analyze the chemical composition of the degradation products.

2.8 | Corrosion rate based on microCT

The Avizo software (Thermo Fischer Scientific, Massachusetts, USA) was used to register microCT datasets of the wires prior to and after immersion to each other using the *Image Registration Wizard* tool. Datasets were binarized using the *Auto thresholding* tool. Datasets were then cropped to remove the extremities of the wires to obtain equal length of the pieces of wire imaged prior to and after immersion. Finally, the *Label Analysis* tool was used to compute the area and volume of each piece of wire. The volume loss due to immersion of each piece of wire was computed.

The CR was determined using the volume-loss method:

$$CR = \frac{\Delta V}{At}$$

CR is the corrosion rate ($\text{mm}\cdot\text{year}^{-1}$ or mmpy), ΔV is the volume loss (mm^3), A is the exposed surface area (mm^2), and t is the exposure time (years).

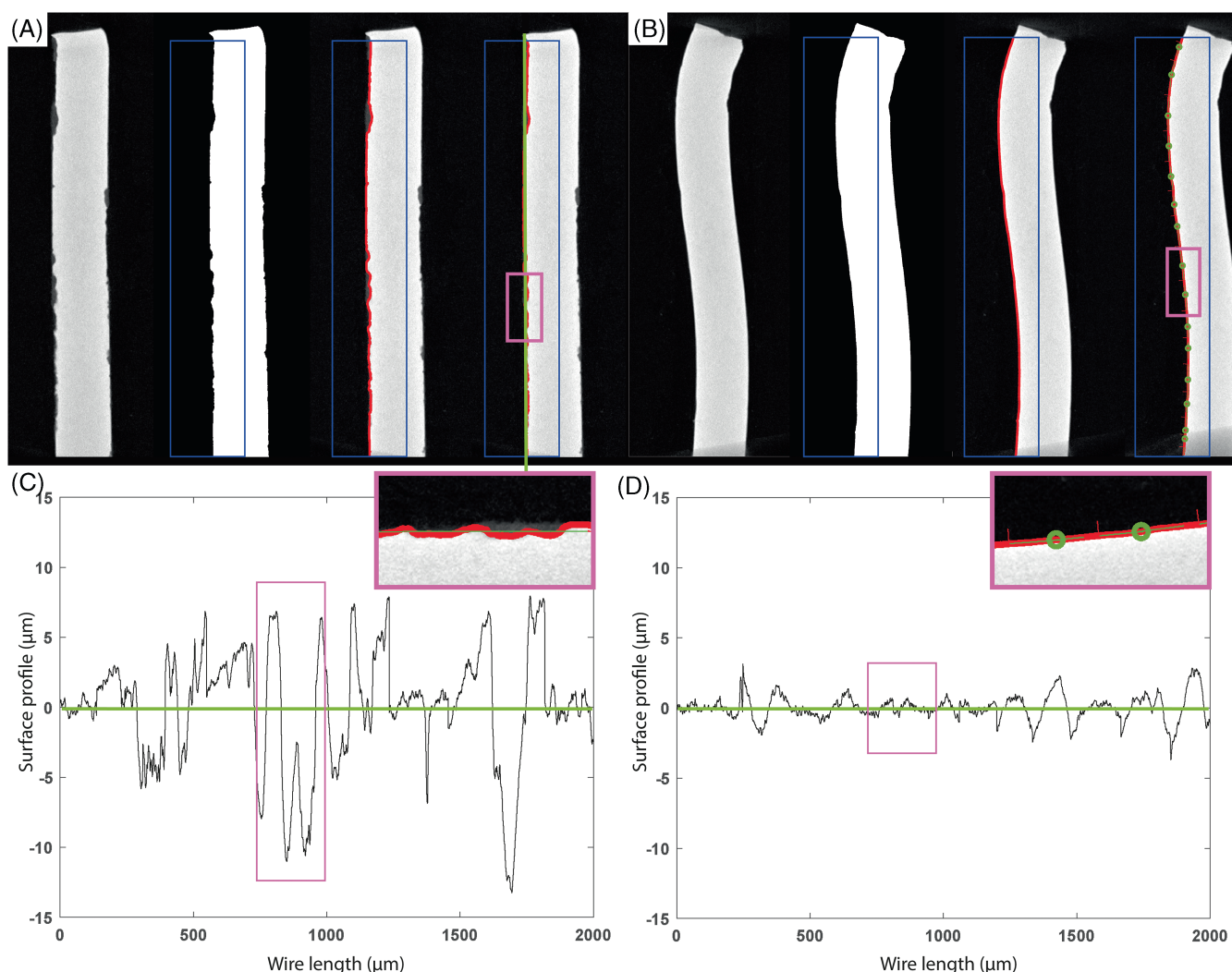


FIGURE 2 Output example of the in-house developed Matlab tool for 2D roughness analysis. (A, B) For two different wires: Original microCT-based longitudinal cross-section, binarized section with ROI selection (blue box), surface detection inside ROI indicated by red line, and baseline detection inside ROI indicated by green line/dots. (C, D) Surface profile over wire length (black curve) for wires in A and B respectively, baseline is indicated in green. In (A, C) a linear baseline for a straight wire was used and in (B, D) a spline baseline (piecewise polynomial function between green dots) for curved wire was used.

2.9 | Statistical analysis

GraphPad prism 9 (GraphPad Software, California, USA) was used for statistical analysis and data visualization. Normality and homoscedasticity of the residuals were checked. When more than two different groups were compared, a one-way ANOVA was applied, followed by Šidák's multiple comparisons test. A Kruskal-Wallis test was applied when normal distribution could not be assumed, followed by Dunn's multiple comparisons test. When the effect of two independent variables (i.e., material type and time) on one third variable (i.e., corrosion rate or roughness) was investigated, a two-way ANOVA was applied, followed by Šidák's multiple comparisons test. When data was not normally distributed, a Kruskal-Wallis test was performed to investigate the effect of each variable separately, followed by Dunn's multiple comparisons test. *P*-values below .05 were considered to be significant; not significant (no star) $p > .05$, $*p \leq .05$, $**p \leq .01$, $***p \leq .001$,

$****p \leq .0001$. In the bar graphs, the mean value of the different samples is indicated by the height of the bars and individual values are also represented. Error bars represent the standard deviation.

3 | RESULTS

3.1 | Differences in corrosion behavior were visualized in full 3D and the corrosion products were identified

Visual differences in corrosion behavior between Co—Cr, Fe, Zn, and the quinary Zn alloy were observed 1, 4, and 7 days after immersion on 3D microCT-based representations of the wires and on 2D cross-sections (Figures 3 and 4). As expected, the Co—Cr alloy is stable and does not degrade over time. For the biodegradable metals, the

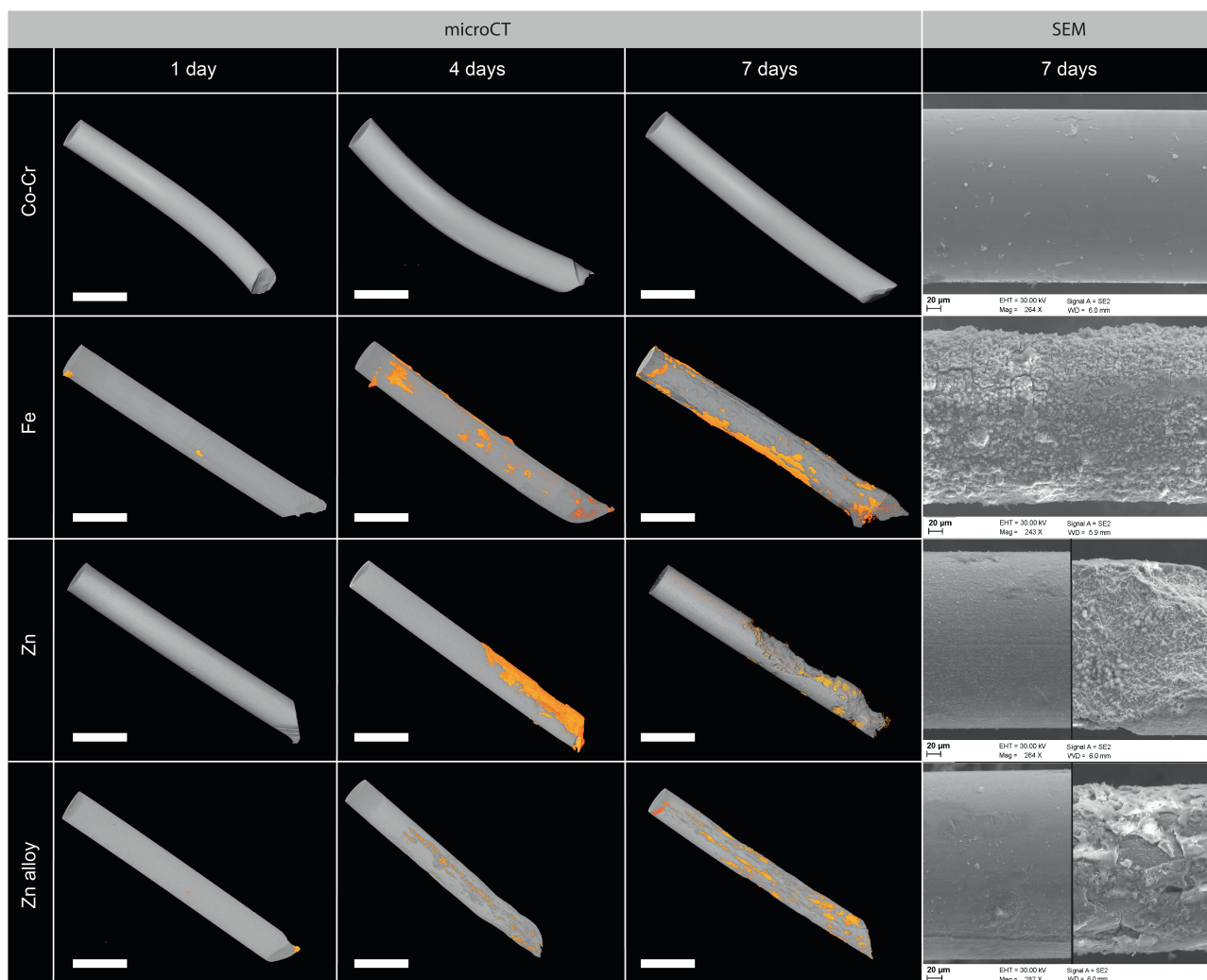


FIGURE 3 Comparison of Co—Cr alloy, Fe, Zn, and Zn alloy after immersion for 1, 4, and 7 days. A representative microCT-based 3D rendering is given for each time point and a SEM image of the wire surface is given for the 7-day time point. Corrosion products are represented in orange in the microCT renderings, scalebars = 400 μm for microCT and 20 μm for SEM.

corrosion products were segmented from the microCT images (represented in orange in Figures 3 and 4). The corrosion products form an oxide layer on the surface of the wire as confirmed by the EDX analysis of the surface of Fe and Zn (Figure 4), which is why they have lower X-ray attenuation and appear with lower gray values than the original metal in the microCT images. They can also be observed in video 1, showing microCT-based transversal cross-sections over the full length of each wire type. For Fe, after 1 day, there were almost no structural changes compared to the control wire. Over time, the wire degraded slowly and homogeneously (Figure 3). The degradation of Fe was wide and shallow (Figure 4). For pure Zn and the Zn alloy there was almost no structural change after 1 day of immersion (Figure 3). Thereafter, degradation of the wires increased, with local deep pitting corrosion for Zn. (Figure 3). For the Zn alloy, the corrosion was more homogeneous along the length of the wire, even though there were regions that were much less corroded than others (Figure 3). SEM images showed that the corrosion occurred preferentially in the darker phase (Zn phase), which means that the alloy phase (lighter phase

where Ag is mostly present) slowed down the corrosion (magnified regions of the Zn alloy in Figure 4). Hence, the alloying has produced deficiencies, as this led to the formation of deep dendrites.

3.2 | The corrosion behavior of the different metal types was compared quantitatively using surface profile lines determined based on the microCT images

The fundamental added value of microCT is that it permits the assessment of a large 3D volume, rather than just a 2D cross-section or a small region of the wire surface. This enables a determination of whether the corrosion is homogeneous or heterogeneous across the length of the wire (Figure 5). The variation in the surface profile was measured (Figure 5D). The Co—Cr alloy, used as a biostable control, showed no significant degradation or change in surface properties, as demonstrated in Figures 3 and 4, supporting its role as a stable benchmark. Based on our measurements of the surface profile from

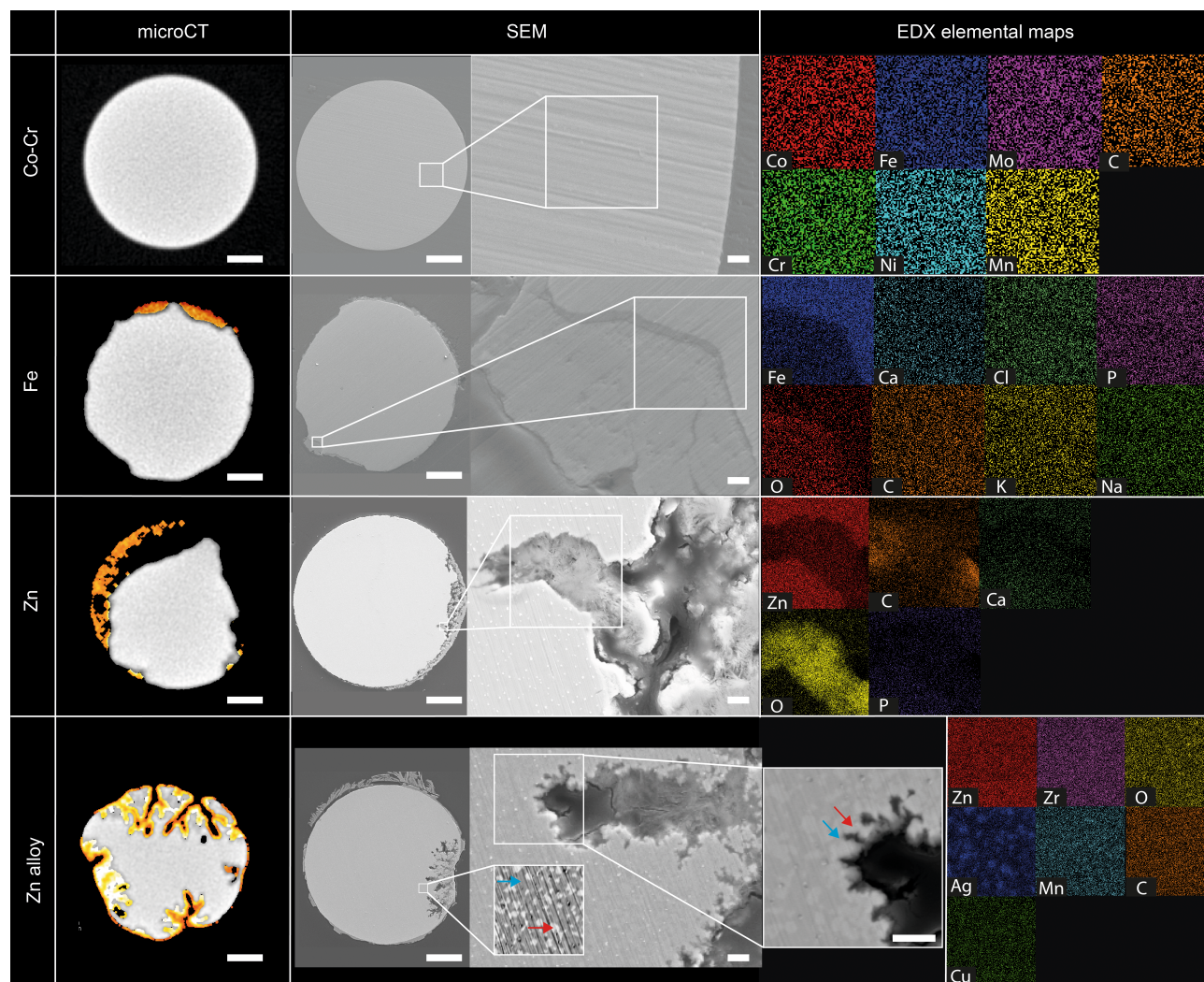


FIGURE 4 Detection of corrosion products of wires after 7 days of static immersion. Co—Cr alloy, Fe, Zn, and Zn alloy transversal cross-sections imaged with microCT and SEM, and EDX elemental maps of corroded and non-corroded regions. Corrosion products are represented in orange in microCT cross-sections. Red arrow = light phase (alloy), blue arrow = dark phase (Zn). Scalebars = 50 μm for cross-sections, scalebars = 2 μm for magnified regions.

the images, we concluded that pure Fe undergoes superficial degradation, characterized by low average values for the peaks and valleys, indicating that the corrosion is predominantly at the surface (Figure 5A,E). Pure Zn exhibits a more pronounced degradation pattern, characterized by higher peaks and deeper valleys, along with significant variation between samples, suggesting that the corrosion of pure Zn is less uniform across different samples (Figure 5B,E). For some of the Zn wires, no degradation was visible on the part of the wire that was imaged. The Zn alloy has mean values of peaks and valleys in between Fe and Zn, indicating a corrosion behavior that is more uniform than pure Zn but more pronounced than the superficial degradation of Fe (Figure 5C,E). The standard deviation gives a quantitative measure of surface variability. The low standard deviation for Fe indicates that the peaks and valleys do not vary a lot and, hence, that the surface is smoother and more regular. For Zn, the standard deviation is higher with also a large variation between samples, indicating high variation especially for samples with higher

values of the mean, suggesting that as the average surface irregularity increases, so does the heterogeneity of the surface profile. The Zn alloy has a standard deviation between Fe and Zn, exhibiting a balance between the smoother surface profile typical of Fe and the higher variability associated with Zn (Figure 5F). However, no significant differences between any of the metal types were observed, both in mean and standard deviation of the peaks and valleys, due to the variations between wires of the same metal type and due to the limited number of samples analyzed.

3.3 | Corrosion rate could be accurately determined by calculating the microCT-based volume loss of the wires

The corrosion rate was computed based on the volume loss using the microCT-based 3D datasets and this was related to the measured ion

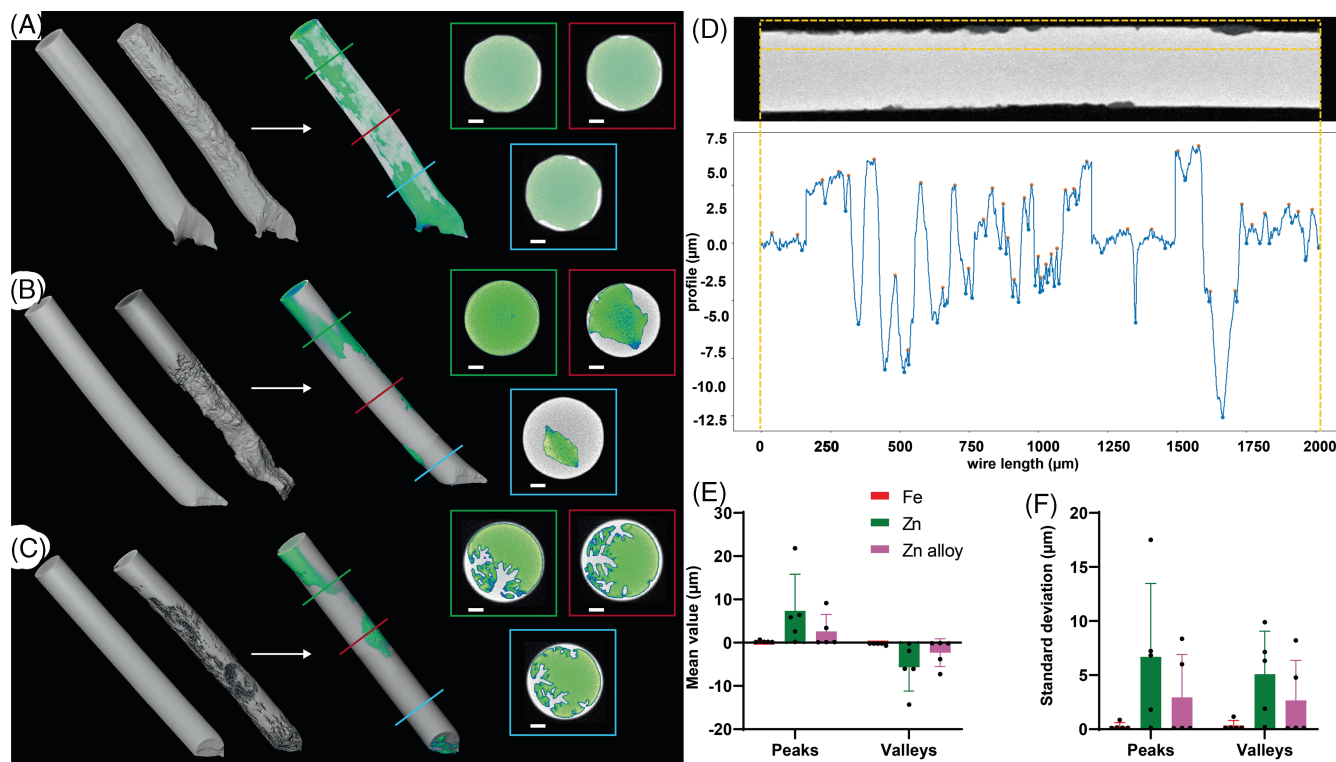


FIGURE 5 Typical degradation behavior of (A) Fe, (B) Zn, and (C) Zn alloy. Right of the arrows gray represents the wire at time point 0 and green represents the wire after immersion. (D) Typical wire longitudinal cross-section with corresponding surface profile (peaks = orange dots, valleys = blue dots), only peaks above 0 and valleys below 0 were considered. (E) Mean value and (F) standard deviation of the peaks and valleys of the surface profile for all metal types. Scalebars = 50 μm, $p > .05$ (ns), $n = 5$.

concentration in solution (Figure 6). Although the absolute corrosion rates obtained from both methods are not the same, the trends are similar (Figure 6A–F). The two methods are in agreement, as shown by the Bland–Altman plot (Figure 6G). This plot compares corrosion rate measurements from microCT and ICP, showing their agreement. The bias (black dotted line at 0.01938) indicates a small average difference between methods. The limits of agreement (red dotted lines at ± 0.91277) outline where 95% of the differences lie, reflecting the consistency between the methods. A random scatter of points around the bias line suggests uniform agreement across measurements. The ion released concentration of Co–Cr in solution was below the detection limit, and hence the corrosion rate was set to 0 (Figure 6A–C). The volume loss of the Co–Cr wires was small, and inaccuracies in the segmentation and registration of the datasets led to some variations and negative values of corrosion rate (Figure 6D–F). The corrosion rate stayed constant over time for Fe and remained below 0.3 mmpy for both measuring methods (Figure 6A,D). For Zn and Zn alloy, there was an increase in corrosion rate at 4 days (Figure 6B,C,E, F). The spread of the degradation rate was higher for Zn than for the Zn alloy because of the large variations in degradation from one sample to the other, due to heterogeneous corrosion. When comparing the metal types to each other for each time point, using the volume loss method, no significant differences were observed due to large variations, but the highest degradation rate was observed for pure Zn at 4 days (Figure 6H).

3.4 | Changes in surface roughness of the different metal types determined using the surface profile lines

Apart from using the surface profile lines to assess the corrosion behavior homogeneity, we also investigated the surface roughness. The surface roughness of a stent is a key factor in determining biocompatibility. Average and total roughness measurements showed that the largest differences between metal types occurred at the 4-day time point, with a larger average and total roughness for Zn compared to the other metal types (Figure 7A,B). After 7 days, there were no more significant differences between metal types, but large variations between wires of the same material were observed. The increase in roughness was not significant compared to the control samples for all metal types, except for the total roughness of the Zn alloy after 7 days (Figure 7D–I). However, an increase in the average and total roughness of Fe appeared after 7 days (Figure 7D,E), while the roughness of pure Zn increased after 4 days and decreased again after 7 days (Figure 7F,G). To have a better idea of the sharpness of the surface of the wires, kurtosis was also evaluated (Figure 7C). The mean value for kurtosis is above 3 for all materials and all time points, indicating that the roughness distribution has many high peaks and low valleys and is thus irregular. At 4 and 7 days the mean kurtosis value for Zn is higher than for Co–Cr, although not significant, with large variations between the Zn wires, indicating a surface that is sharper than for the other materials.

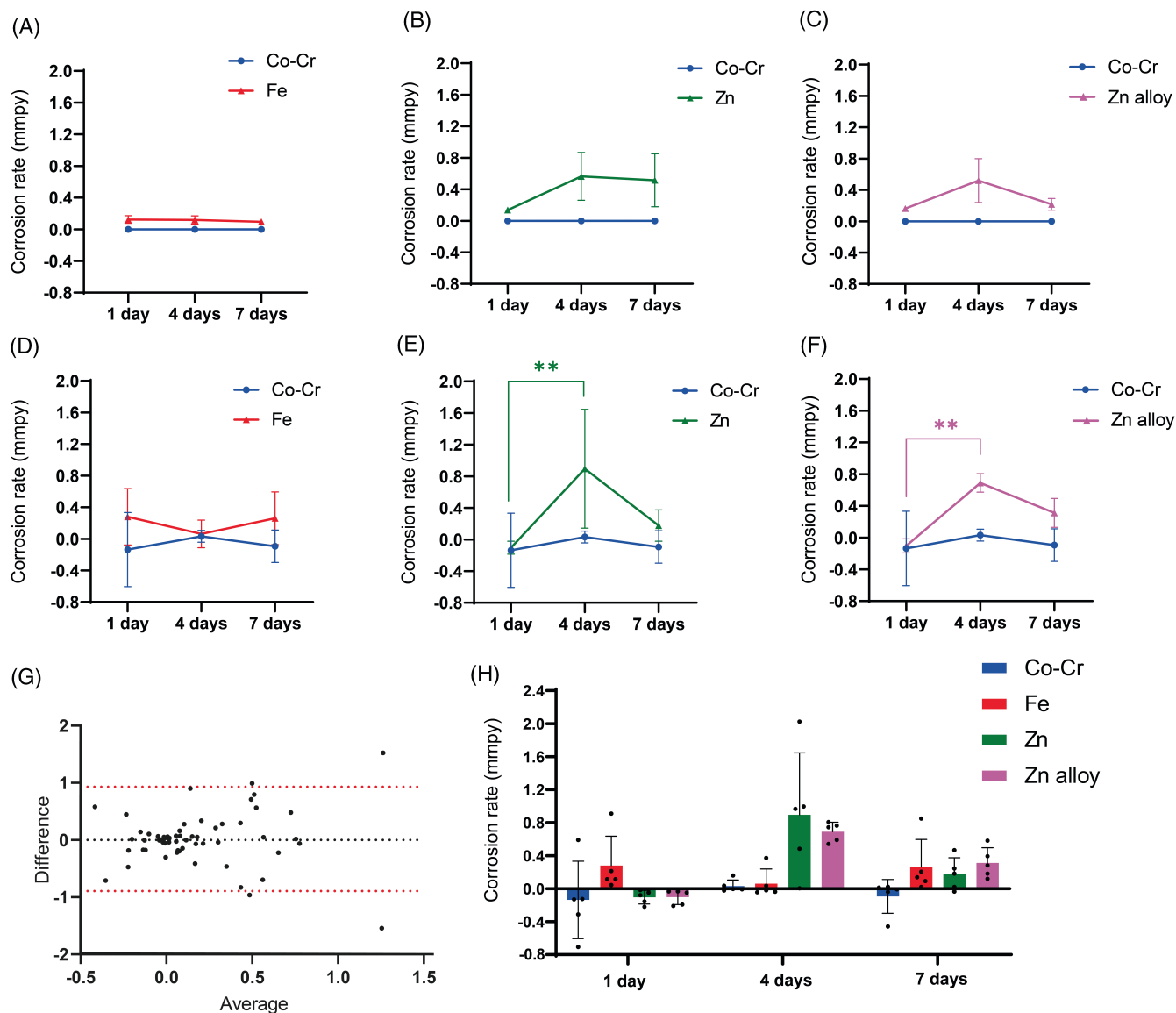


FIGURE 6 Comparison of the corrosion rate of the different metal types at different time points. Corrosion rate evaluated using the ion-released concentration based on ICP-OES comparing Co—Cr with (A) Fe, (B) Zn, and (C) Zn alloy. Corrosion rate evaluated using the volume loss method based on microCT comparing Co—Cr with (D) Fe, (E) Zn, and (F) Zn alloy. (G) Bland–Altman plot comparing both methods (ICP- and microCT-based corrosion rate) with bias = 0.01938. (H) Comparison between Co—Cr, Fe, Zn, and Zn alloy of the corrosion rate at different time points using the volume loss method. ns $p > .05$, * $p \leq .05$, ** $p \leq .01$, $n = 5$.

4 | DISCUSSION

When developing new biodegradable alloys for intravascular stent applications, there are several targets in terms of corrosion rate, corrosion behavior, and surface properties. The degradation rate of Fe-based materials is considered to be too low while Mg-based alloys have a degradation rate that is too high.³² Zn is a newcomer within the biodegradable metals and has a corrosion rate that is higher than that of Fe and lower than that of Mg, being a good compromise between both.³⁶ However, the mechanical strength of Zn needs to be enhanced and this can be done through alloying. The challenge is to find the optimal elemental composition without compromising its

positive qualities in terms of biocompatibility and degradation rate. That is why in vitro screening studies of different metal types are crucial.

The present study aimed at establishing a method to evaluate the corrosion behavior and surface properties in a more detailed and accurate 3D manner than existing techniques, such as mass loss measurements or polarization experiments. We used high-resolution microCT imaging with a voxel size of 1 μm . This level of detail in the imaging process allowed for a more detailed evaluation of the corrosion rate across different metal types and the 3D imaging provided information on the implant as a whole as opposed to only 2D sections or small regions of interest, as in the case with SEM imaging.^{37,38} We

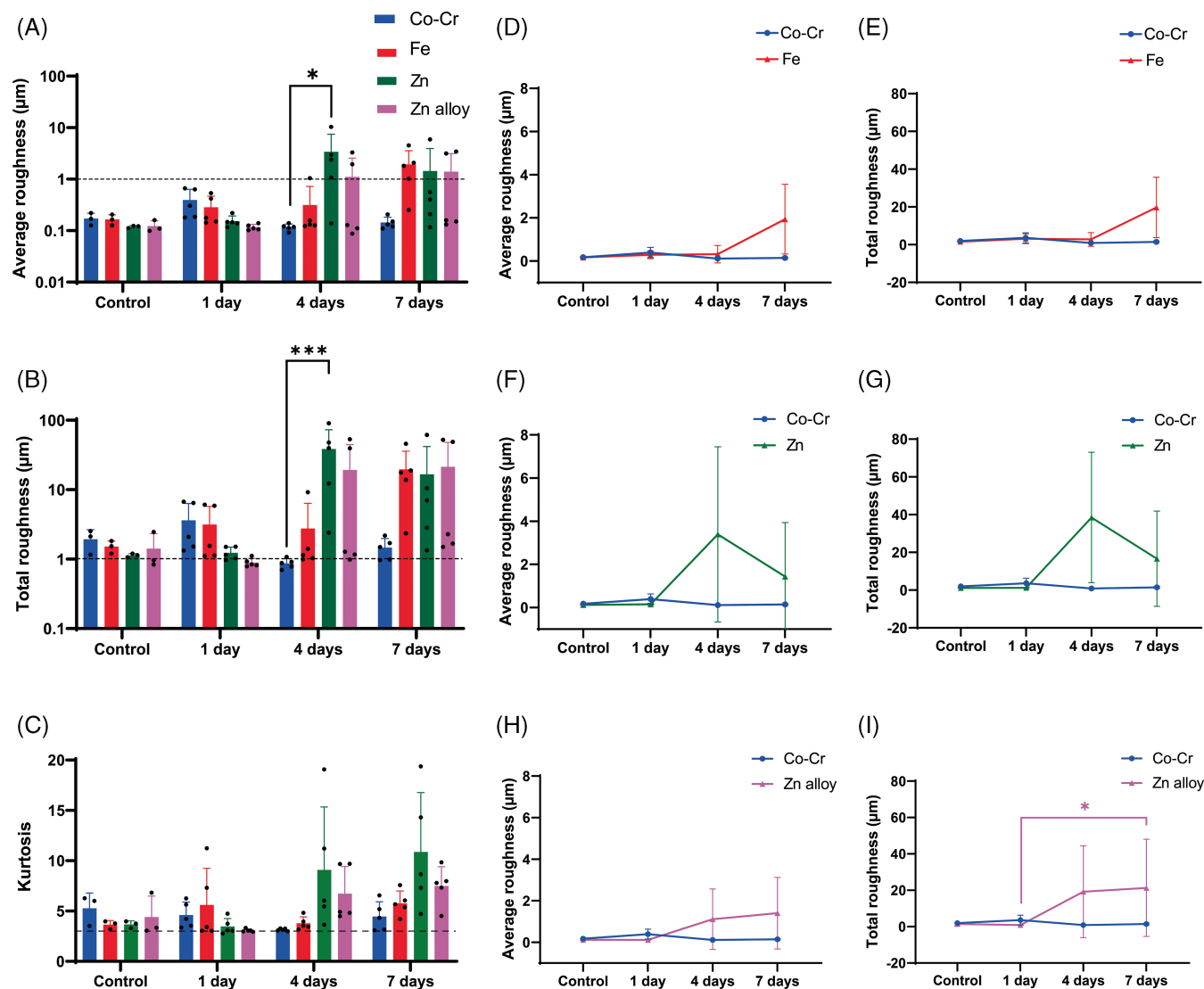


FIGURE 7 Comparison of the surface roughness of the different metal types at different time points. MicroCT-based (A) average roughness (Ra), (B) total roughness (Rt), and (C) Kurtosis (Rku) for Co—Cr, Fe, Zn, and Zn alloy for the control samples and after 1, 4, and 7 days of immersion. The dotted line at $Y = 1 \mu\text{m}$ in (A) and (B) represents the detection limit because of microCT dataset voxel size. The dotted line at $Rku = 3$ in (C) represents the limit between a bumpy ($Rku < 3$) or spiky ($Rku > 3$) surface. Comparison of the average roughness (Ra) between Co—Cr and (D) Fe, (F) Zn, and (H) Zn alloy and comparison of the total roughness (Rt) between Co—Cr and (E) Fe, (G) Zn, and (I) Zn alloy. ns $p > .05$, * $p \leq .05$, ** $p \leq .01$, *** $p \leq .001$, $n = 5$.

improved an existing surface roughness measurement tool³⁵ to compute the roughness parameters relative to an adaptable baseline for both straight and curved wire geometries. The surface roughness parameters of the implants can be used to explain the corrosion behavior in a more quantitative way and provide more information on the biocompatibility of the materials. We complemented our results with two already well-established techniques: ICP-OES and SEM-EDX. The corrosion rate computed through the ion loss concentration based on ICP measurements allowed us to validate our volume-loss microCT-based technique. SEM-EDX allowed us to compare the corrosion behavior observed in our microCT images, and it enabled the chemical identification of corrosion products. The latter is not possible with standard microCT. The microCT images allowed to differentiate

between the base metal and the corrosion product layer. This differentiation was crucial as it allowed to exclude the corrosion products from our corrosion rate calculations, thereby improving the accuracy of our measurements. In the ICP-OES approach, as not all corrosion products were effectively removed from the metal surface prior to measurement of the ion released concentration, this potentially led to an underestimation of the actual corrosion rates. To address this challenge and improve the precision of corrosion rate assessments with ICP-OES in the future, it is important to fully remove the corrosion product layer, using, for example, chemical methods. In this case, it is important to remove all corrosion products without compromising the integrity of the underlying base material, highlighting the advantage of using microCT imaging to compute the corrosion rate.

In terms of corrosion behavior, the ideal material should degrade uniformly and at the surface. Pitting, the formation of dendrites, or any preferential corrosion should be avoided to prevent fragmentation and premature failure of the stent. The roughness parameters can be used to better assess and quantify the corrosion behavior. Indeed, we found that the surface roughness of the different metals was closely related to the corrosion behavior and rate. High variation in the roughness surface profile and in average and total roughness between samples also meant higher variations in corrosion rate. Considering that the Co–Cr was the biostable reference, our analysis confirmed that its average and total roughness, and its degradation rate were close to 0. The Fe wires, which had low average and standard deviation values of peaks and valleys in the surface profile and a low increase in roughness through time, also had the lowest corrosion rate and a low variability in corrosion rates across samples. This corrosion mode is believed to be ideal, being uniform and indicating a consistent corrosion behavior across the samples. The pure Zn had the highest variation in its surface profile (high peaks and low valleys and high variation in their standard deviation), and high variation between samples for average and total roughness. It also exhibited the highest variation in corrosion rate across samples. This behavior indicates that Zn is subject to more pronounced variations in corrosion behavior and hence, uneven surface degradation. Indeed, it exhibits heterogeneous deep pitting corrosion and could promote the detachment of larger pieces of metal in the blood circulation if this occurs too quickly *in vivo*, which could lead to serious complications, such as embolism. Zn also presented a high value of kurtosis, indicating that the surface of the wires was sharp. As a smooth surface is believed to reduce platelet activation and aggregation, a sharp surface could potentially induce platelet activation, thrombosis, and neointimal proliferation.³⁹ The Zn–Ag–Cu–Mn–Zr alloy, which was in between Fe and Zn regarding the mean and standard deviation values of the peaks and valleys in the surface profile also experienced an increase in average and total roughness that was between Fe and Zn and corrosion rate values between Fe and Zn, with less variation across samples than Zn. We did observe preferential corrosion in the alloy phase compared to the Zn phase. To solve this deficiency, a solution heat treatment could be applied to the metal to increase the dispersion of the second phase, as observed by Guillory et al.⁴⁰ Such a treatment has also been shown to improve mechanical properties (tensile strength and ductility). Nevertheless, this novel Zn alloy, with superior mechanical properties and inflammation-resistant characteristics also showed improved corrosion behavior compared to pure Zn with more homogeneous corrosion and less pitting. The detailed 3D investigation of this alloy, which had not been done before, provides beneficial information on the corrosion behavior at high resolution, giving new insights for further investigation of new and improved Zn alloys. Understanding the relationships between corrosion rate and surface roughness allows for a better and more quantitative interpretation of corrosion behavior and highlights the importance of controlling surface roughness in mitigating corrosion. Additionally, the roughness measurements provide information on the biocompatibility of the material. Increased surface roughness due to corrosion can potentially

enhance endothelial cell adhesion and proliferation, which is beneficial for the healing process around a stent. However, excessive roughness or irregular corrosion products could potentially lead to adverse biological responses, including inflammation or thrombosis.^{23,24}

We have also identified some limitations to our study. The microCT data offers valuable high-resolution 3D information on the corrosion behavior of the metals. However, it is limited by the fact that it cannot provide other crucial microstructural information, such as grain size, grain orientation, and electrochemical behavior. Such microstructural details are essential for a deeper understanding of the variations in corrosion behavior across different metal types. This limitation highlights the need for complementary analytical techniques, such as more in-depth SEM analysis or electron backscatter diffraction (EBSD) to better understand the underlying mechanisms driving corrosion processes. These techniques can be applied after microCT thanks to its non-destructive character. Moreover, as we decided to work on high-resolution microCT images (1 μm isotropic voxel size) to accurately measure the surface roughness and volume loss of the samples, we only acquired images of a small portion of each wire. This means that the ICP-based corrosion rate was computed on the entire wire, while the volume loss method corrosion rate was based on a small portion of each wire. However, the corrosion rate remained similar, meaning that the smaller portion of wire represented the behavior of the entire wire relatively well. Additionally, the same location was assessed in each wire (the lower 2 mm of each wire) to balance out any effects of location on the wires. In the future, however, it would be interesting to image and compute the volume loss of multiple areas of interest for each wire. Moreover, we found that comparing the absolute corrosion rate values obtained here with those from other studies in the literature remains challenging, as the rates from *in vitro* immersion tests reported vary significantly based on specific experimental conditions (immersion solution used, static versus dynamic conditions, time points examined, method use for computing the corrosion rate).^{19,41–45} In our case, we have performed static immersion tests because it has been shown in the past that dynamic immersion testing (solution agitation or shaking) fails to replicate accurately the *in vivo* behavior. Indeed, the presence of blood flow tends to slow down the degradation process by forming a protective passivation layer, composed of corrosion products, on the metal surface, thereby mitigating rapid degradation.³² This is in contrast with dynamic immersion testing, which has been observed to accelerate degradation rates, differing from the natural *in vivo* environment.⁴³ However, dynamic immersion testing might have allowed to minimize localized effects, such as pH changes. Finally, we did not do a follow-up study of the same wires over time because different wires were used for each time point. However, this could be easily done in the future as microCT is a non-invasive technique.

In the future, the same microCT-based technique can be applied to acquire images of explanted wires that have been implanted in an animal model, such as in Refs. 20,32,46–48. In these studies, classical 2D histological cross-sections were obtained to evaluate biocompatibility and interactions between the tissue and the metallic implant.

However, only limited cross-sections were available per sample due to the labor-intensive technique and the requirement of special cutting methods to section the metal. With 3D microCT, the location of interest can be readily selected, and further analysis can provide more insights into important properties, such as homogeneous versus heterogeneous corrosion behavior. The biocompatibility could also be assessed by measuring the volume of the neointimal growth that surrounds the wire or implant.

5 | CONCLUSION

Overall, this study provides insights into the corrosion behavior of biodegradable metallic alloys for intravascular stent applications and proposes an optimized microCT-based technique for evaluating corrosion rate, behavior, and surface properties from in vitro immersion tests. The results could potentially inform and accelerate the development of more effective biodegradable materials for use in medical devices.

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DATA AVAILABILITY STATEMENT

The microCT datasets generated and/or analyzed during the current study are not publicly available due to their considerable size but are available from the corresponding author on request.

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