

Implants and contact allergy: are sensitizing metals released as haptens from coronary stents?

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Summary

Background. The possible impact of metal release from coronary artery stents has, with their increased use, become a concern.

Objectives. To study *in vitro* metal release in biologically relevant milieu from coronary stents made of different alloys.

Materials and method. Coronary stents in common use in a department of cardiology at the time of the study were tested. A previously described *in vitro* technique was used, whereby the stents were kept in the extraction media for a week. Two different extraction media were used to show the necessity of studying the actual biological surrounding of the implant when metal release is investigated. Metal release was determined with atomic absorption spectrometry.

Results. In this study, we show metal release from stents after immersion in extraction media of artificial sweat and cysteine solution, as illustrative media.

Conclusion. Metal release from coronary stents is shown. The magnitude of release is influenced by several factors. The extent to which metal release *in vitro* has potential biological effects, in terms of elicitation of an allergic reaction or induction of sensitization, *in vivo* needs to be explored. However, as metal release from an implant in a biologically appropriate medium has been established, better risk assessments in relation to delayed hypersensitivity may be undertaken.

Key words: contact allergy; implant; metal release; stent.

We are exposed to metals at home and at work. These common exposures and the fact that metals, when ionized, are able to penetrate the skin and possibly act as haptens and induce an allergic contact reaction make exposure an important issue. There are prerequisites for sensitization and the elicitation of an allergic contact reaction (1). With regard to ionization of the metal, the local environmental

conditions are critical; when the metal is in contact with skin, sweat on the skin surface and the skin surface itself are important for ionization (2). Exposure to metals in implants makes it possible for sensitization to occur, possibly through metal ions in, for example, saliva or blood (3–7). This implies that, when ionization is considered, not only sweat but also blood and the composition of surrounding tissue should be taken into account, making a general model for ionization, elicitation or possible sensitization more complex.

In a previous publication, we described a model for studying metal release from gold, indicating the need, when the ionization of gold is considered, to carefully decide which extraction media to use, taking account of

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where the gold is to be used *in vivo*. In the present study, we have focused on stents used for percutaneous coronary intervention (PCI).

Stents can be made of several different metals and alloys, and also be coated in different ways, making the question of what will be a hapten and the evaluation of possible relevance more difficult.

In the present study, we analysed a selection of bare metal stents, used at the time of the study in the Department of Cardiology at Skåne University Hospital, Malmö, and performed the analyses according to existing models for analysis of nickel release from objects intended to be in contact with the skin and the release of gold from gold-containing items (8, 9).

The aim of this study was to investigate the release of metals from metal stents and the possibility of haptenization.

Materials and Methods

Stents

The stents are described in detail in Table 1. Stainless steel 316L is described in detail in Table 2. The aim was to investigate metal release from different types of stent, but the choice of brand was limited by what was actually available in the Department of Cardiology at Skåne University Hospital, Malmö during the 12 months during which the stents were collected. The stents used were those that, for some reason, could not be put into patients (e.g. loss of sterility). The Helistent[®] was chosen as a representative of the numerous brands of pure 316L bare metal stents. The Nir Royal[®] and Titan2[®] were the only gold-plated and titanium–nitride oxide-plated stents, respectively, that were or had been available in Sweden, and the Driver[®] was considered to be a good representative for the increasing number of cobalt–chromium stents. When the experiments were performed, the intention was to have an area of contact with the extraction medium that was roughly similar for all stent brands. For this reason, for analysis, two stents of the same brand were used together from all of the manufacturers except for the Driver[®], the chromium-containing stent, as the length of this stent was almost double that of the others. It should be emphasized that only an approximation of the area of contact with the extraction medium could be calculated, as the stents from different manufacturers differ in design, making exact calculation of the area difficult. Before testing, the stents were expanded by inflation of the stent balloon to nominal burst pressure (simulating actual use); this changed the area of contact. Throughout the experiments, room temperature was constant.

Solutions

Artificial sweat (11, 12), consisting of deionized water, 0.5% (vol/vol) sodium chloride (Acros Organics, Morris Plains, NJ, USA), 0.1% (vol/vol) lactic acid (Sigma Chemical Co., St Louis, MO, USA), and 0.1% (vol/vol) urea (Sigma Chemical Co.), was prepared as previously described (11). The pH was adjusted with ammonia (NH₃) (Scharlau Chemie, Barcelona, Spain). The solution was kept in the refrigerator. Solutions of 0.1 M cysteine (ICN Biomedicals, Aurora, OH, USA) were prepared in deionized water (8, 9). For the amino acid solution, the pH was adjusted with nitric acid (Scharlau Chemie, Sentmenat, Spain). For the preparation of standards, standard solutions for gold (BDH Laboratory Supplies, Poole, UK), nickel, chromium, and cobalt (all from Merck, Darmstadt, Germany), corresponding to 1000 ppm metal, were diluted in Suprapur[®] nitric acid (Merck). Ethanol (Kemetyl, Haninge, Sweden) was used for cleaning of the stents before extraction.

Metal release procedure

The stents were pretreated by cleaning them in ethanol for 60 min. All experiments were performed with one extraction.

- 1 The stents were kept in 3.1–5.1 ml (different volumes, owing to the size of stents) of artificial sweat (pH 6.4) for a week.
- 2 The stents were placed in polypropylene tubes, and 3.1–5.1 ml (different volumes, owing to the size of stents) 0.1 M cysteine solution (pH 7.4) was added. The test tubes were placed on a rocker, and constantly shaken gently for 7 days at room temperature (~21°C). After a week, a white precipitate was found in the cysteine solutions, believed to consist of cystine, a dimer of cysteine. The precipitate was dissolved before analysis by the addition of 100 µl of concentrated nitric acid.

Chemical analysis

The extraction medium was analysed for nickel, cobalt, chromium and gold with an atomic absorption spectrometer. The spectrometer used was an AAnalyst 800 (Perkin-Elmer, Norwalk, CT, USA) equipped with a graphite furnace and hollow cathode lamps. Sample analysis was performed with Zeeman background correction. Details of the analysis of each metal are shown in Table 3. Samples were diluted in 0.5 M nitric acid, and 20 µl of each sample was injected. Standard samples (0–0.05 ppm of each metal) were prepared by diluting the standard solutions in 0.5 M nitric acid.

Table 1. Specifications of the different stents used in this study

Stent number	Stent type	Alloy	Metal components in the alloy*	Plating	Stent diameter (mm)	Stent length (mm)
1	Helistent [®]	SS 316L	Fe, Mn, Cr, Ni, Mo, Cu	None	3.0	13
2	Helistent [®]	SS 316L	Fe, Mn, Cr, Ni, Mo, Cu	None	3.0	16
3	Titan2 [®]	SS 316L	Fe, Mn, Cr, Ni, Mo, Cu	Titanium nitride	2.75	13
4	Titan2 [®]	SS 316L	Fe, Mn, Cr, Ni, Mo, Cu	Titanium nitride	2.75	13
5	Nir Royal [®]	SS 316L	Fe, Mn, Cr, Ni, Mo, Cu	Gold, 99.9%	3.0	16
6	Nir Royal [®]	SS 316L	Fe, Mn, Cr, Ni, Mo, Cu	Gold, 99.9%	3.0	16
7	Driver [®]	CoCr F562	Fe, Cr, Ni, Mo, Ti, Co	None	3.0	30

SS 316L, stainless steel 316L; CoCr F562, cobalt–chromium F562.

Fe, iron; Mn, manganese; Cr, chromium; Ni, nickel; Mo, molybdenum; Cu, copper.

*Information on the alloys from: <http://www.medtronic.com/newsroom/content/1110132739468.pdf>. Accessed August 2013, where 316L is compared to the Driver[®] stent.

Table 2. Stainless steel 316L; chemical requirements for metals; heat analysis (10)

Element	Composition (%)
Manganese	2.00 maximum
Chromium*	17.00–19.00
Nickel	13.00–15.00
Molybdenum*	2.25–3.00
Copper	0.50 maximum
Iron [†]	Balance

*The compositional requirement is as follows: % chromium + 3.3X % molybdenum > 26.0.

[†]Approximately equal to the difference between 100% and the sum percentage of the other specified elements. The percentage iron content by difference is not required to be reported.

Table 3. Instrumental settings and instrumental limit of detection (LOD) for metal analysis with atomic absorption spectrometry

Metal	Wavelength (nm)	Bandwidth (nm)	Modifier	Instrumental LOD (µg/ml)
Ni	232.0	0.2	No	0.001
Cr	357.9	0.7	15 µg of Mg(NO ₃) ₂	0.001
Co	242.5	0.2	15 µg of Mg(NO ₃) ₂	0.001
Au	242.8	0.7	No	0.004

Ni, nickel; Cr, chromium; Co, cobalt; Au, gold.

Results

The results regarding stents and the release of gold, nickel, chromium and cobalt in artificial sweat and cysteine are shown in Table 4.

Much less metal was released from the plated stents than from the non-plated stents, and, for the gold-plated stents, release of chromium, nickel and cobalt was not detected, either in artificial sweat or in cysteine solutions.

The highest cobalt release was found for the Driver[®], which is known to contain cobalt.

In cysteine solution, release was in the same range as found in artificial sweat for nickel, chromium, and cobalt.

A great amount of gold, the plating metal used for one of the plated stents, was released (500 times more than for any of the other metals, if calculated in µg/stent).

Discussion

The use of implants in our bodies is increasing. Therefore, it is important to know whether an implant contains a material that the patient may be allergic to or whether allergy may be induced.

Delayed hypersensitivity (as in contact allergy) as such is not a disease, but, when an individual is exposed to the allergen at a sufficient dose, an allergic reaction will develop. Extracutaneous reactions may be seen (7, 13–15), and, regarding implants, these are of particular interest. There are a number of case reports on aseptic implant loosening (orthopaedic implants), sterile osteomyelitis, and persistent swelling (16), as well as dermatological reactions such as dermatitis and urticaria. Cardiotoxicity has been discussed as a systemic effect of metal release from implants (17). The processes of contact allergy and other reactions to implants are not fully understood (15). Retrospective studies have shown a correlation between contact allergy to gold and restenosis following PCI and stent procedures (18, 19). There is some evidence that there may be a risk of allergic reactions resulting from the release of haptens from implant surfaces (7, 13–15). The crucial step for sensitization and elicitation with regard to metal implants is ion formation (7).

The most attractive way to evaluate the side-effects of implant materials is through prospective studies in animals and humans. However, there is a problem with animal studies (the total exposure being different, and studies often being unethical or not feasible in humans).

Regarding contact allergy and possible reactions to implants, we consider that this may, at least in part,

Table 4. Metal release after extraction in solution for 1 week

Stent	Extraction medium	Metal release			
		Ni (µg/stent)	Cr (µg/stent)	Co (µg/stent)	Au (µg/stent)
	Artificial sweat				
Helistent® 316L		0.026	0.036	< 0.002*	< 0.006*
Titan2® 316L		< 0.002*	0.003	< 0.002*	< 0.006*
Nir Royal®		< 0.002*	< 0.002*	< 0.002*	< 0.008*
Driver® Co–Cr		0.037	0.010	0.093	< 0.020*
	Cysteine				
Helistent® 316L		0.009	0.012	< 0.002*	< 0.006*
Titan® 316L		0.004	0.003	< 0.002*	< 0.006*
Nir Royal®		< 0.002*	< 0.002*	< 0.002*	28.5
Driver® Co–Cr		0.059	0.037	0.052	< 0.020*

Extraction media: artificial sweat, pH 6.4, 3.1–5.1 ml (different volumes, owing to size of stents) and 0.1 M cysteine, pH 7.4, 3.1–5.1 ml. Concentrations of metals in the extraction solution were measured with atomic absorption spectrometry. Data are presented as amount (µg) of metal released per stent

*Below limit of detection. Instrumental limit of detection (LOD): Ni, 0.001 µg/ml; Co, 0.001 µg/ml; Cr, 0.001 µg/ml; Au, 0.004 µg/ml. LOD calculated as µg/stent from: (instrumental LOD, µg/ml) × (extraction volume, ml)/(number of stents). Extraction volumes: Helistent® 316L, 3.1 ml; Titan2® 316L, 3.1 ml; Nir Royal®, 4.1 ml; Driver®, Co–Cr 5.1 ml. Two stents were extracted, except for Driver® Co–Cr (one stent).

be evaluated by first studying ionization/metal release, determining whether the hapten is a weak or a strong sensitizer, and then estimating the total exposure, which may be highly relevant, especially for metals such as gold.

In the present study, we have shown that there is corrosion of gold-plated stents, and that even titanized stents corrode, albeit with a very small amount of metal release. The plating as such is protective in relation to the release of metal from the underlying alloy, but the metal used for plating is very important with regard to corrosion. The extraction medium is important (20). In our previous study, we showed that gold is released from a cysteine-containing extraction medium but not when artificial sweat is used, indicating the importance of studying the biological environment where the metal is used when deciding on which extraction medium to use (9). We have also previously shown that the solution used for extraction (i.e. *in vivo*, the medium/tissue surrounding the implant) will be decisive for how much release there will be (9). The study also indicates that the same metal may react differently when present in different alloys (2).

It would have been preferable to correlate metal release with the patch test dose. Here, we only tried to estimate the dose with regard to gold, giving rise to the highest metal release. If the Nir Royal® stent is approximated as a metal wire net, the total surface area can be approximated as ~0.84 cm². With a metal release of 28.5 µg gold/stent per week, this corresponds to gold release of 34.1 µg/cm² per week. The patch test concentration of gold in 20 mg of gold sodium thiosulfate 2% pet., when tested with Finn Chambers® (area of 0.5 cm²), equals a surface concentration of ~300 µg gold/cm². However, making the correlation is difficult, for several reasons:

- (1) The stent area is difficult to calculate (see above).
- (2) The surrounding tissue will also change, because, when the stent is dilated, it will actually dilate the vessel and cause trauma to the underlying intima. Thus, the stent will, in part, be adjacent to a traumatized intima, and in part be adjacent to the circulating blood; then, over time, the intima will heal and overgrow the stent, and the metal will no longer be in direct contact with the circulating blood. How this changes metal release and what the area of exposure actually is during the different phases are difficult to determine.
- (3) It must also be taken into account that, with gold, we know that it is not only the dose on the test chamber that decides the strength of the contact allergic reaction, but also the total dose supplied through circulating haptens (21). Thus, even if release is small, one would, in practice, have to consider the total exposure.

What is a strong or a weak sensitizer? It is important to evaluate this, especially when thinking of new materials for implants: cobalt, for example, is considered to be a strong sensitizer, whereas nickel is a weak one, but, again, exposure becomes the most important issue.

What is known about exposures to the metals that we have evaluated here? It is necessary to consider the frequency of contact allergy in a population that is related to both exposure and allergen potency. The frequency of contact allergy to nickel in the general population is high, the estimate being up to 17% among females and 3% among males (22), although the frequencies have decreased because of the nickel legislation (23). For

chromium and cobalt, the frequency is 1–3% (13, 24), and in patients with dermatitis it is even higher. For gold, the frequency differs between studies, but is usually approximately 5–19% in dermatitis patients (25–29). For many metals that are known to be included in alloys used for implants (e.g. titanium and molybdenum), the frequency of contact allergy in dermatitis patients or in the general population has not been adequately studied.

A fourth aspect that may be of importance as implants become increasingly common is how the individual is exposed to metal ions. For gold, there are clear associations between contact allergy, dental materials, and age (30, 3), whereas for nickel there is a clear association with piercing (31). There are data indicating that there seems to be less contact allergy to nickel in individuals exposed to dental braces in youth (prior to piercing) (32, 33). This indicates the importance of considering what is known about the allergen (there are several differences between gold and

nickel, for example), the total exposure, and possibly the order of exposures. The fact that the implant may itself induce contact allergy (20) makes this evaluation even more important.

Conclusion

In these *in vitro* experiments, we have shown metal release from metal coronary artery stents. The amount of metal released depends on the extraction medium, stent, and metals used. The extent to which metal release *in vitro* has potential biological effects, in terms of elicitation of an allergic reaction or induction of sensitization, *in vivo* needs to be explored. However, now that metal release from an implant in a biologically appropriate medium has been established, better risk assessments in relation to delayed hypersensitivity may be undertaken.

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