

Evaluation of metal allergies in patients with coronary stents

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In-stent restenosis is a complication which impairs the success of coronary stenting. Recently, it was supposed that a delayed hypersensitivity reaction to nickel and molybdenum might be one of the triggering factors in in-stent restenosis. We have analyzed the data collected in our centre with respect to this hypothesis. Altogether, 34 patients were investigated (24 male, 10 female). Patch tests were performed with the standard series of the German Contact Dermatitis Research Group and a metal series containing the metal components of 316 L stainless steel. A positive patch test reaction to nickel was observed in 4 (11.8%) patients. None of the patients showed sensitization to the other metals. Retrospective analysis was performed in 20 patients: 2 of these patients had a positive patch test reaction to nickel, one of whom had an in-stent restenosis, and the other not. Restenoses were predominantly observed in patients with negative patch test reactions to nickel (6/18 patients). Out of the patients who were investigated prospectively only one showed sensitization to nickel. Restenosis was observed in 2 patients: neither patient had nickel allergy. Although it still cannot be excluded that metal allergy may play a role in the restenosis process in coronary stenting, there is at present little evidence for it.

Key words: 316 L stainless steel, coronary stent; delayed hypersensitivity reaction; in-stent restenosis; metal allergy; nickel; patch test; stent. © Blackwell Munksgaard, 2002. © Blackwell Munksgaard, 2002.

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In recent years, metallic implants have become increasingly important in cardiology due to the technique of coronary stenting. In-stent restenosis is a complication which impairs the success of this effective method. In in-stent restenosis, histopathologically an inflammatory and fibroproliferative infiltrate is found (1, 2). Recently, it was supposed by Köster *et al.* (3) that a delayed hypersensitivity reaction to nickel and molybdenum might be part of the inflammatory process and one of the triggering factors in in-stent restenosis. We have analyzed the data collected in our centre with respect to this hypothesis.

Patients and Methods

Patients

Patch tests were performed in patients who were admitted to the Department of Cardiology for coronary (re-)angiography. Altogether 34 patients were investigated (24 male, 10 female).

Retrospective analysis was performed in 20 patients. Patch testing was initiated when the patients

were admitted to the clinic for follow-up reangiography at least 3 months, and mostly 6 and 12 months, respectively, after stenting. One patient, who had repeatedly shown in-stent restenoses was seen for patch testing for the first time 22 months after the first stent implantation. Data of all patients in this group were evaluable.

In 14 patients, patch testing was performed prior to their first coronary catheterization or intervention. All patch tests performed were evaluable. In 4 patients, it was determined during catheterization that the implantation of a stent was not necessary, and 3 patients were lost to follow-up. Therefore, only 7 patients were evaluable in this group observed prospectively.

Methods

Coronary angiography and patch testing were performed independently by different investigators in the Departments of Cardiology and Dermatology, respectively. The collected data were not analyzed until the patient was discharged from the clinic.

Table 1. Patch test preparations of the 316 L stainless steel metals

Metal	Patch test substance	Patch test concentration/vehicle	Supplier
Nickel	Nickel sulfate	5.0% pet.	Hermal ^a
Chromium	Potassium dichromate	0.5% pet.	Hermal
Manganese	Manganese sulfate	2.0% pet.	HAL ^b
Molybdenum	Ammonium heptamolybdate	1.0% aq.	Hermal

Pet., petrolatum, aq., aqua. ^aReinbek, Germany. ^bDüsseldorf, Germany.

Significant restenosis was defined as a $\geq 50\%$ diameter lumen reduction within the stent area. Patch tests were performed with the standard series of the German Contact Dermatitis Research Group (DKG) and a metal series containing the metal components of 316 L stainless steel.

The patch test preparations were applied to the upper back for 24 h, preparations being supplied by Hermal (Reinbek, Germany) and HAL (Düsseldorf, Germany) (Table 1). Patch tests were read on days 1–3 (24, 48 and 72 h) after patch test application. Only data of patients in whom the 72 h patch test reading had been performed were evaluated. The patch test reactions were, according to the criteria of the German Contact Dermatitis Research Group (4), considered positive if they were +, ++ or +++ on day 3 (72 h). Informed consent was obtained from all patients.

Results

A positive patch test reaction to nickel was observed in 4 (11.8%) patients. None of the patients showed sensitization to the other metals of 316 L stainless steel.

In the group of the patients analyzed retrospectively (Table 2), 10% (2 patients) showed sensitization to nickel. An in-stent restenosis was observed in 7 patients (35%). The restenoses occurred in 6 out of 18 patients (33.3%) having no sensitization to nickel and in one of the 2 patients (50%) who were sensitized to nickel. The latter patient was a 68-year-old man suffering from three-vessel disease who had had a bypass operation with grafts to the left anterior descending and the left circumflex coronary arteries in 1991 and who in November 1997 received 3 stents (2 Devon stents, 1 Sito stent) because of significant right coronary artery ste-

nosis. Within the following 9 months after stenting he developed 3 in-stent restenoses, which were successfully treated with laser and percutaneous transluminal coronary angioplasty, respectively. In March 1999, a relapse was treated with a Multilink stent in-stent implantation. After this intervention he had a very good long-term result, no restenosis being observed during coronary angiography one year later. Sensitization to nickel was first demonstrated in September 1999, the point in time when he was sensitized not being known. Only one patient of the group who was investigated prospectively showed sensitization to nickel (Table 3). Restenosis was observed in 2 patients (29%). Neither patient had nickel allergy.

Discussion

Coronary stents are mostly made from 316 L stainless steel, which contains the metals nickel, chromium, molybdenum and manganese (5). Within the patch-test population of the Information Network of Departments of Dermatology (IVDK) nickel is the most frequent allergen, showing sensitization rates of 13–17% (6, 7). Within the IVDK in 1995 22.3% of women were positive, but only 5.8% of men (6). In the German population the nickel sensitization rate amounts to 13.1%, also with more women (20.4%) than men (5.8%) (8). Sensitization to chromium (potassium dichromate) is less frequent than to nickel, in the German population a rate of 1.1% being found (8). Within the IVDK between 1992 and 1999, 787 patients were patch tested with 1% ammonium heptamolybdate, only 3 of whom (0.38%) were positive (9). Between 1999 and 2001 we have patch tested 199 patients with 2% manganese sulfate in our department, none of whom have been positive.

Table 2. Results of the retrospective analysis (no. of patients)

In-stent restenosis	Nickel allergy		
	No	Yes	Total
No	12	1	13
Yes	6	1	7
Total	18	2	20

Table 3. Results of the prospective analysis (no. of patients)

In-stent restenosis	Nickel allergy		
	No	Yes	Total
No	4	1	5
Yes	2	0	2
Total	6	1	7

In their retrospective study of 131 patients, Köster *et al.* (3) found 11 positive patch test results in 10 patients. Sensitization to nickel was observed in 7 (5.3%) and sensitization to molybdenum in 4 (3.1%) patients. In-stent restenosis ($\geq 50\%$ diameter stenosis) was found in 89 patients. All 10 patients in whom positive patch test reactions had occurred were in the restenosis group. The nickel sensitization rate in our investigation of 11.8% was slightly lower than in the German population, which is explained by the predominantly male collective. In the patients analyzed retrospectively, 2 patients (10%) had a positive patch test reaction to nickel, one of whom had an in-stent restenosis, and the other not. Moreover, restenoses were predominantly observed in patients with a negative patch test reaction to nickel. Also in contrast to Köster *et al.* (3), we did not find any patient with a positive reaction to molybdenum. The different results may be due to different patch test preparations having been used. In the investigation of Köster *et al.* (3), patch testing was performed with 0.5% molybdenum chloride, whereas we applied 1% ammonium heptamolybdate (10). In contrast to nickel and chromium, patch testing with other metals such as molybdenum and manganese is less standardized and thus more prone to irritant reactions (11). The case history of the patient who was sensitized to nickel and in whom recurring restenoses were observed did not enable the point in time when he was sensitized to be determined. If sensitization had already been acquired before the first stenting in 1997, the restenoses might be related to the nickel allergy, whereas nickel sensitization induced after March 1999 would not be relevant. The case demonstrates the methodological problems of a retrospective analysis in answering the question if metal allergy may be causative for the in-stent restenosis process. This problem was also discussed by Keane *et al.* (12) when considering the study of Köster *et al.* (3).

Metallic implants have been used for many years. Cutaneous allergic reactions to metallic implants are well documented. Eczematous dermatitis is mostly observed but urticarial, bullous and even vasculitic eruptions and cutaneous angiomatosis have also been reported (13–15). Eczema may be localized to the skin overlying the metallic implant, present at distant sites or widespread (5, 13, 16, 17). It may not resolve until the implant has been removed (16, 17). To our knowledge, there have been no reported cases of localized or widespread dermatitis after coronary stenting, though recently a widespread eczema was reported in a patient who had received an aortic endoprosthesis (18). Overall, there is little doubt that metallic implants can elicit an allergic contact derma-

titis, but it is still under discussion whether sensitization to the metals of an implant may affect implant performance or even cause endoprosthesis failure (19, 20). There have been reports of patients being exposed for several years to orthopaedic implants containing a metal to which they were allergic, but showing no orthopaedic complications (21). Nevertheless, Thomas *et al.* (22) recently reported a patient with aseptic loosening of an orthopaedic chromium/cobalt alloy, in whom patch testing showed sensitization to potassium dichromate and investigation of the peri-implantar tissue demonstrated an oligoclonal T-cell infiltrate and expression of a Th1-type cytokine profile.

In summary, metal allergy may play a role in the failure of metal implants, but further investigations need to be carried out. It also cannot be excluded that metal allergy may play a role in the restenosis process in coronary stenting, but at present there is little evidence for this. Prospective multicentre studies are needed to answer the following questions: (a) Is the in-stent restenosis rate higher in patients with sensitization to the metal(s) of the stent that will be implanted (especially nickel) than in nonsensitized patients? (b) Is there a higher incidence of metal allergy in patients receiving coronary stents in comparison to patients treated by angioplasty? (c) Does the prognosis of patients who develop metal sensitization after stent implantation differ from patients who do not develop metal sensitization (especially with respect to in-stent restenosis)?

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