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Does nickel allergy play a role in the development of in-stent restenosis?

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Abstract. – *Objectives:* **It was suggested that coronary in-stent restenosis might be triggered by allergy to nickel and molybdenum ions released from stainless-steel stents. We sought to explore any possible relationship between nickel allergy and in-stent restenosis.**

Materials and Methods: **50 patients were studied, who underwent elective follow-up coronary angiography for recurrent symptoms after prior coronary stenting, at least 3 months following the index procedure. Consecutively, we enrolled 25 patients with ≥ 50% in-stent restenosis (study group), and 25 others with < 50% restenosis (control group), as revealed by coronary angiography. Evaluation for nickel allergy was performed using 5% nickel sulphate solution in petroleum applied as a patch test to the interscapular region by the Finn chamber method. A positive test was defined as an inflammatory response with erythema, edema, papulovesicles, or infiltration after 48 or 72 hours.**

Results: **The mean age of the whole study cohort was 55.9 ± 13.9 years, 44 (88%) being males. Two patients of the study group (8%) had a history of contact allergy to metals. However, both of them showed a negative patch test result. No patient in the control group had a history of metal allergy ($p > 0.05$). Only one patient in the study group (4%) had a positive patch test result for nickel contact allergy, whereas all patients in the control group had a negative result ($p > 0.05$).**

Conclusions: **Based on the available evidence, a cause-effect relationship between nickel allergy and in-stent restenosis cannot be confirmed.**

Key Words:

In-stent restenosis, Nickel allergy, Coronary stenting.

Introduction

Percutaneous coronary angioplasty is nowadays the most widely used means of myocardial revascularization[1]. The implantation of metal stents during percutaneous coronary intervention has markedly reduced the frequency of acute complications and improved patient outcome[2]; although, except in the setting of acute myocardial infarction[3], survival has not been significantly improved. Yet, in-stent restenosis (ISR) still remains the "Achilles heel" of this advanced technology.

ISR occurs in 20-30% of patients undergoing stent implantation; it is caused entirely by neointimal proliferation[4,5] in which inflammation plays a pivotal role. The inflammatory milieu depends on systemic and local (arterial) factors. In this context, diabetes mellitus, vessel morphology (such as vessel diameter, lesion length, the amount of residual plaque burden)[6,7] and procedural factors (such as vessel wall trauma) may all augment ISR.

One retrospective study suggested that allergic reactions to nickel and molybdenum ions released from stainless-steel coronary stents may be among the triggering mechanisms of ISR[8]. It recommended, therefore, that stainless-steel stents should be avoided in patients with metal ions hypersensitivity, either reported on clinical history or proven by skin patch test. In the current study, any possible correlation between ISR and hypersensitivity to nickel ions released from stainless-steel stents, was explored.

Patients and Methods

Patient Selection

50 patients admitted to the cardiac catheterization laboratory during the period from August 2008 to February 2009 were studied. These patients underwent elective follow-up coronary angiography for recurrent symptoms after prior coronary stenting, at least 3 months following the index procedure. We included only patients who had received 316 L stainless-

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steel slotted-tube balloon-expandable stents. Patients presenting with acute coronary syndrome, those who had received drug-eluting stents or stents based on other metal alloys (for example: chromium-cobalt stents), those with autoimmune diseases (for example: rheumatoid arthritis), those with immunosuppressive diseases (for example: HIV), those receiving immunosuppressive medications (such as corticosteroids and cytotoxic drugs), and those with severe skin lesions that would interfere with patch test results, were excluded. Before inclusion, an informed written consent was obtained from each patient after full explanation of the study protocol, and the protocol was reviewed and approved by the local institutional human Research Committee as it conforms to the ethical guidelines of the 1964 Declaration of Helsinki, as revised in 2002. Proper clinical history was taken with special emphasis on allergy to metal contact and allergic skin diseases (such as contact dermatitis, urticaria, etc.).

Evaluation for Nickel Hypersensitivity

Evaluation for nickel allergy was performed using 5% nickel sulphate solution in petroleum (Hermal Kurt Herrmann GmbH & Co. OHG, Reinbeck, Germany) applied as a patch test to the interscapular region by the Finn chamber method. The test was performed and analyzed according to the International Contact Dermatitis Research Group[9]. Hypersensitivity reaction was evaluated by an experienced dermatologist 48 hours, and when necessary 72 hours following patch application. A positive test result was defined as an inflammatory response with erythema, edema, papulovesicles, or infiltration after 48 or 72 hours.

Follow-up Coronary Angiography

All patients underwent selective left and right coronary arteriography using the standard technique, and the angiographic data were individually analyzed by an interventional cardiologist blinded to both patch test results and clinical data. Angiographic ISR was defined as 50% diameter stenosis (by visual estimation) within the stent or in the 5-mm distal or proximal segments adjacent to the stent, at follow-up coronary angiography. Based on the above definition, 25 consecutive patients with ISR at follow-up coronary angiography were enrolled as the "study group", and 25 consecutive patients without ISR were enrolled as the "control group".

Statistical Analysis

All continuous variables were presented as mean ± SD, if they were normally distributed. Data were tested for normal distribution using the Kolmogorov-Smirnov test. Categorical variables were described with their absolute and relative frequencies (percentages). Comparisons between the 2 study groups were performed using unpaired *t*-test and Pearson's Chi-Square test for the distribution of continuous and categorical variables, respectively. All tests were two-sided and a probability value < 0.05 was considered statistically significant. Analyses were performed with Statistical Package of Social Sciences version 12.0 (SPSS Inc., Chicago, IL, USA).

Results

Baseline Patient Characteristics

50 patients were enrolled in the current study, which include 25 consecutive patients with ISR at follow-up coronary angiography (study group) and 25 consecutive patients without ISR (control group). Table I shows baseline clinical characteristics of the whole study cohort, as well as the 2 individual study groups. The mean age of the whole study cohort was 55.9±13.9 years, 44 (88%) being males. The mean period elapsed since the last stenting procedure was 17±4.3 months. The 2 individual study groups were statistically matched regarding age, gender, diabetes mellitus, hypertension, family history of ischemic heart disease, history of prior acute coronary syndrome and history of contact allergy to metals. Two patients in the study group (8%) had a history of contact allergy to metals; however, both of them showed a negative patch test result. No patient in the control group had a history of contact allergy to metals. Nevertheless, patients with ISR were more frequently smokers [21 (84%) versus 13 (52%), respectively, $p = 0.028$], and included more patients with dyslipidemia [19 (76%) vs 5 (20%), respectively, $p < 0.001$], as compared to those without ISR.

Data of Previous Stents Implanted

The cohort of 50 patients had previously received a total of 71 stents: 32 patients had only one stent each; 15 who had 2 stents each; and 3 who had 3 stents each. Comparison between the 2 study groups regarding the mean diameter and mean length of the first, second and third stents (when

Table I. Baseline characteristics of the whole study cohort and the 2 individual study groups.

	Whole cohort (N = 50)	Study group (N = 25)	Control group (N = 25)	p
Age (years)	55.9 ± 14	55.2 ± 9	56.5 ± 8	> 0.05
Males	44 (88)	23 (92)	21 (84)	> 0.05
Smoking	34 (68)	21 (84)	13 (52)	< 0.05
Diabetes mellitus	20 (40)	13 (52)	7 (28)	> 0.05
Hypertension	31 (62)	16 (64)	15 (60)	> 0.05
Dyslipidemia	24 (48)	19 (76)	5 (20)	< 0.001
Family history of IHD	6 (12)	3 (12)	3 (12)	> 0.05
History of prior ACS	13 (26)	8 (32)	5 (20)	> 0.05
History of contact allergy to metals	2 (4)	2 (8)	0 (0)	> 0.05

All continuous variables are presented as mean ± SD, while categorical variables are presented as numbers (percentage).
ACS: acute coronary syndrome; IHD: ischemic heart disease.

available), is presented in Table II. The mean diameter of the first stent was significantly lower in the study group as compared to the control group (3.01±0.16 mm vs 3.17±0.29, respectively, p = 0.023). Otherwise, as in Table II, no statistically significant difference was found between the 2 groups concerning the mean diameter of the second or third stents, or the length of any stent.

Skin Patch Test Results

Only one patient in the study group (4%) had a positive patch test result for nickel contact allergy; whereas all patients in the control group had a negative test result (p = 0.5).

Discussion

In the current study, any possible relationship between ISR and hypersensitivity to nickel ions in patients treated with stainless-steel stent implantation, was found. The existence of such a relationship was not supported by the results of the current study.

Stent implantation adds an iatrogenic factor that enhances neointimal hyperplasia, the so called 'response-to-foreign-material hypothesis'. Metallic implants can induce electron exchange (redox reaction), proton exchange (hydrolysis), or complex formation (metal ion-organic molecule binding) in living tissues[10]. The resultant protein (e.g. fibrinogen) activation, cell toxicity, fibroblast growth stimulation, platelet, monocyte/macrophage, endothelial cell adhesion, and endothelial cell migration[10] may all contribute to the occurrence of restenosis.

Stainless-steel used to produce stents (316 L) is made of iron fortified with carbon and contains significant amounts of nickel (12%), chromium (as chromate) (17%) and molybdenum (2%). Ions of these elements elute from the stents and

Table II. Data of previous stents implanted in the 2 individual study groups.

	Study group (N = 25)	Control group (N= 25)	p
Mean diameter of the 1st stent (mm)	3.01 ± 0.16	3.17 ± 0.29	< 0.05
Mean diameter of the 2nd stent (mm)	2.97 ± 0.23	3.05 ± 0.16	> 0.05
Mean diameter of the 3rd stent (mm)	3.25 ± 0.4	3	> 0.05
Mean length of the 1st stent (mm)	19.7 ± 4.3	18.9 ± 3.9	> 0.05
Mean length of the 2nd stent (mm)	19.7 ± 4.5	18.4 ± 2.7	> 0.05
Mean length of the 3rd stent (mm)	17.7 ± 2.5	18	> 0.05

All continuous variables are presented as mean ± SD, while categorical variables are presented as numbers (percentage).
ACS: acute coronary syndrome; IHD: ischemic heart disease.

might induce the above mentioned reactions[10]. Moreover, inflammatory/allergic reactions that form new tissue around metallic alloys containing nickel are well known in patients with dental and orthopaedic implants[11]. Since nickel was shown to cause skin contact allergic dermatitis in 5% of males, and 15% of females[8], it is likely that stents which contain nickel (and other elements) would enhance neointimal hyperplasia.

Köster et al[8] enrolled 131 patients prior to undergoing follow-up coronary angiography for suspected ISR following the implantation of stainless-steel stents. All patients underwent allergy patch testing for nickel, chromate, molybdenum, manganese and stainless-steel. Of the 89 patients who had ISR, 10 (11%) had a positive patch test result [7 (7.9%) patients had a positive reaction to nickel, and 4 (4.5%) had a positive reaction to molybdenum]. Forty-two patients did not have restenosis and none of them had a positive patch test.

In accordance with the results of the current study, other studies failed to demonstrate a correlation between metal allergy and ISR in patients treated with stainless-steel stents[12-14]. Nevertheless, Iijima et al[14], have shown that despite the absence of a relationship between metal hypersensitivity and ISR, it was a powerful predictor for the recurrence of ISR – after its initial treatment - by multivariate analysis. As they concluded, it may be that the mechanism of restenosis is different between initial stent implantation and subsequent dilatation of ISR.

A possible limitation of the current study is the low rate of metal allergy in the cohort (2%) that did not adequately permit to hold a reliable comparison between the study group and the control group. Nickel contact allergy is more common in women; among women, it decreases significantly with age[15]. Considering the fact that females constituted only 12% of the current series, with a mean age 55.9±13.9 years for the whole series, it is not surprising to find such a low rate of nickel allergy. Previous studies on metal allergy in patients with ISR reported a higher prevalence of metal allergy (6.9-11.8%) than the current one[12-14]. Racial variations may explain this divergence of findings; environmental and genetic factors might also be implicated.

The skin patch test for nickel contact allergy is simple and inexpensive. Unfortunately, a significant percentage of patients with a clinical history of nickel allergy show a negative patch test result[16], a fact which, to a large extent, limits the sensitivity of the commercially available skin patch test. It was previously noted that 5% nickel sulphate may give false negative reactions, and alternative test substances like 5% nickel chloride can, therefore, be useful in selected cases[17]. Likewise, modified skin patch testing techniques that employ pretreatment of the test area, were described, and demonstrated increased rates of positive reactions to 5% nickel sulphate patch test[16,18]. Two patients in the current series had a history of contact allergy to metals; both of them, however, showed a negative patch test result. Thus, it is probable that patients allergic to nickel were underestimated in the current series due to the limited sensitivity of the currently employed skin patch test.

Clinical Implications

The recently introduced 'bioactive' stents coated with titanium-nitride-oxide which completely prevents discharge of nickel, chromium and molybdenum ions, have been a breakthrough in stent technology. The safety of the titanium-nitride-oxide-coated stents has been confirmed in real-life unselected populations[19,20]. Interestingly, bioactive stents have demonstrated an even "better" outcome as compared to paclitaxel-eluting stents in the real-world setting of "high risk" patients and complex (type B and C) coronary lesions[21], as well as in patients presenting with acute myocardial infarction[22]. Possible contributors to these favorable results of bioactive stents are the low electrochemical surface potential and the prevention of nickel and other ion discharge.

Limitations of the Study

The current findings are based on a single-center study with a relatively small sample size of the cohort, a fact that makes it difficult to generalize our results to all patients with previously implanted stainless-steel stents. Multicenter studies employing the same protocol and examining a larger number of patients are obviously needed. Another subgroup of patients with chromium-cobalt stents, in which the concentration of nickel is higher than the investigated stents, should also be included as a comparison group. The limited sensitivity of the currently employed skin patch test and the low prevalence of nickel hypersensitivity in the

whole series might constitute obvious limitations. Other limitations of this study include the retrospective design of the study and the possibility of selection bias, since we studied a cohort of patients referred for follow-up coronary angiography after prior angioplasty with stenting, most likely due to recurrent symptoms. Another important concern is that the response of endothelial and vascular smooth muscle cells to metals might be different from that of epidermal cells. In this regard, it is recommended to study the effect of nickel and molybdenum specifically on these cell lines (in terms of proliferation), in order to provide a direct evidence for the role of these metals in restenosis.

In conclusion, based on the results of this study and other available evidence in the literature, a cause-effect relationship between nickel hypersensitivity and ISR, cannot be confirmed.

References

1) Mack MJ, Brown PP, Kugelmass AD, Battaglia SL, Tarkington LG, Simon AW, Culler SD, Becker ER. Current status and outcomes of coronary revascularization 1999 to 2002: 148,396 surgical and percutaneous procedures. Ann Thorac Surg 2004; 77: 761-768.

2) Serruys PW, de Jaegere P, Kiemeneij F, Macaya C, Rutsch W, Heyndrickx G, Emanuelsson H, Marco J, Legrand V, Materne P, Belardi J, Siguart U, Colombo A, Goy JJ, van den Heuvel P, Delcan J, Morel M: for the Benestent Study Group. A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. Benestent Study Group. N Engl J Med 1994; 331: 489-495.

3) Madsen JK, Grande P, Saunamäki K, Thayssen P, Kassis E, Eriksen U, Rasmussen K, Haunsø S, Nielsen TT, Haghfelt T, Fritz-Hansen P, Hjelms E, Paulsen PK, Alstrup P, Arendrup H, Niebuhr-Jørgensen U, Andersen LI. Danish multicenter randomized study of invasive versus conservative treatment in patients with inducible ischemia after thrombolysis in acute myocardial infarction (DANAMI). DANish trial in Acute Myocardial Infarction. Circulation 1997; 96: 748-755.

4) Windecker S, Simon R, Lins M, Klauss V, Eberli FR, Roffi M, Pedrazzini G, Moccetti T, Wenaweser P, Togni M, Tüller D, Zbinden R, Seiler C, Mehilli J, Kastrati A, Meier B, Hess OM. Randomized comparison of a Titanium-Nitride-Oxide-coated stent with a stainless steel stent for coronary revascularization: The TiNOX trial. Circulation 2005; 111: 2617-2622.

5) Dussaillant GR, Mintz GS, Pichard AD, Kent KM, Satler LF, Popma JJ, Wong SC, Leon MB. Small stent size and intimal hyperplasia contribute to restenosis: a volumetric intravascular ultrasound analysis. J Am Coll Cardiol 1995; 26: 720-724.

6) Hoffmann R, Mintz GS, Dussaillant GR, Popma JJ, Pichard AD, Satler LF, Kent KM, Griffin J, Leon MB. Patterns and mechanisms of in-stent restenosis: a serial intravascular ultrasound study. Circulation 1996; 94: 1247-1254.

7) Serruys PW, Kay IP, Disco C, Deshpande NV, de Feyter PJ. Periprocedural quantitative coronary angiography after Palmaz-Schatz stent implantation predicts the restenosis rate at six months: results of a metaanalysis of the BElgian NEtherlands Stent study (BENESTENT) I, BENESTENT II Pilot, BENESTENT II and MUSIC trials: multicenter ultrasound stent in coronaries. J Am Coll Cardiol 1999; 34: 1067-1074.

8) Köster R, Vieluf D, Kiehn M, Sommerauer M, Kähler J, Baldus S, Meinertz T, Hamm CW. Nickel and molybdenum contact allergies in patients with coronary in-stent restenosis. Lancet 2000; 356: 1895-1897.

9) Fegert S. Manual of Contact Dermatitis. 2nd ed. Copenhagen: Md Munksgaard; 1981.

10) Steinemann SG. Metal implants and surface reactions. Injury 1996; 27(suppl 3): SC16-SC22.

11) Steinemann SG. Titanium: the material of choice? Periodontology 2000; 17: 7-21.

12) Norgaz T, Hobikoglu G, Serdar ZA, Aksu H, Alper AT, Ozer O, Narin A. Is there a link between nickel allergy and coronary stent restenosis? Tohoku J Exp Med 2005; 206: 243-246.

13) Hillen U, Haude M, Erbel R, Goos M. Evaluation of metal allergies in patients with coronary stents. Contact Dermatitis 2002; 47: 353-356.

14) Iijima R, Ikari Y, Amiya E, Tanimoto S, Nakazawa G, Kyono H, Hatori M, Miyazawa A, Nakayama T, Aoki J, Nakajima H, Hara K. The impact of metallic allergy on stent implantation: metal allergy and recurrence of in-stent restenosis. Int J Cardiol 2005; 104: 319-325.

15) Smith-Sivertsen T, Dotterud L K, Lund E. Nickel allergy and its relationship with local nickel pollution, ear piercing, and atopic dermatitis: a population-based study from Norway. J Am Acad Dermatol 1999; 40: 726-735.

16) Seidenari S, Motolese A, Belletti B. Pre-treatment of nickel test areas with sodium lauryl sulfate detects nickel sensitivity in subjects reacting negatively to routinely performed patch tests. Contact Dermatitis 1996; 34: 88-92.

17) Menne T. Nickel allergy-reliability of patch test evaluated in female twins. Derm Beruf Umwelt 1981; 29: 156-160.

18) Seidenari S, Manzini BM, Belletti B. Pretreatment of the test area with 1-day occlusion improves

the response rate to NiSO4 5% pet. patch tests in subjects with a positive history of nickel allergy. Contact Dermatitis 1995; 33: 152-156.

19) Karjalainen PP, Ylitalo A, Airaksinen KE. Real world experience with the TITAN stent: a 9-month follow-up report from the Titan PORI registry. EuroIntervention 2006; 2: 187-191.

20) Mosseri M, Tamari I, Plich M, Hasin Y, Brizines M, Frimerman A, Miller H, Jafari J, Guetta V, Solomon M, Lotan C. Short and long term outcome of the Titanium-NO stent registry. Cardiovasc Revasc Med 2005; 6: 2-6.

21) Karjalainen PP, Annala AP, Ylitalo A, Vahlberg T, Airaksinen KE. Long-term clinical outcome with titanium-nitride-oxide-coated stents and paclitaxel-eluting stents for coronary revascularization in an unselected population. Int J Cardiol 2010; 144: 42-46.

22) Karjalainen PP, Ylitalo A, Niemelä M, Kervinen K, Mäkikallio T, Pietilä M, Sia J, Tuomainen P, Nyman K, Airaksinen KE. Two-year follow-up after percutaneous coronary intervention with titanium-nitride-oxide-coated stents versus paclitaxel-eluting stents in acute myocardial infarction. Ann Med 2009; 21: 1-9.