

Cobalt release from implants and consumer items and characteristics of cobalt sensitized patients with dermatitis

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doi:10.1111/j.1600-0536.2011.02001.x

Summary

Background. Cobalt allergy is prevalent in dermatitis patients. Very little documentation exists about current sources of cobalt exposure.

Objectives. To investigate and discuss putative sources of cobalt exposure and to present selected epidemiological data on cobalt allergy from patch-tested dermatitis patients in an attempt to better understand cobalt allergy.

Materials and methods. 19 780 dermatitis patients aged 4–99 years were patch tested with nickel, chromium or cobalt between 1985 and 2010. The cobalt spot test was used to test for cobalt ion release from mobile phones as well as cobalt-containing dental alloys and revised hip implant components.

Results. Six of eight dental alloys and 10 of 98 revised hip implant components released cobalt in the cobalt spot test, whereas none of 50 mobile phones gave positive reactions. The clinical relevance of positive cobalt test reactions was difficult to determine in the majority of patients. Isolated patch test reactivity to cobalt was less associated with occupational dermatitis and hand eczema than patch test reactivity to cobalt in combination with other contact allergies.

Conclusions. It is often difficult to interpret the relevance of a positive patch test reaction to cobalt, and there is a need for further studies to determine sources of cobalt exposure.

Key words: cobalt allergy; cobalt dermatitis; cobalt ions; epidemiology; screening; spot test.

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Conflicts of interest: Jacob P. Thyssen and Morten S. Jellesen sold the cobalt spot test to SmartHealth (Phoenix, Arizona) after its development, and will receive a royalty fee from annual net sales of the spot test. Torkil Menné, Jeanne D. Johansen, Carola Lidén, Anneli Julander, Peter Jensen, Stig S. Jakobsen, Kjeld Søballe and Klaus Gotfredsen have no conflict of interest to disclose. Funding: Peter Jensen was financially supported by the Michaelsens Foundation.

Accepted for publication 26 August 2011

Cobalt is a strong skin sensitizer (grade 5 of 5 in the guinea pig maximization test) (1). It is therefore not surprising that cobalt allergy is frequent, affecting 6.2–8.8% of patch-tested dermatitis patients within the European Surveillance System of Contact Allergies network (2). Cobalt allergy is typically observed in about 1% of the general population (3), although a recent Danish patch test study including 3460 adults showed that only 0.2% were cobalt-allergic (0.4% of women and 0.1% of men) (4). When the prevalence of contact allergy to a substance is high, sources of exposure need to be identified, to help clinicians determine the clinical relevance of positive test reactions in their patients,

and to help regulators, and others, prevent allergen exposure. Over the years, occupational cobalt exposure has mainly been observed in metal workers, bricklayers, and pottery-workers. Today, cobalt is typically used to make high-temperature corrosion-resistant super-alloys for jet and gas turbine engines, magnetic alloys, electro-deposited alloys, and high-strength steels (5, 6). Accordingly, a recent Swedish study documented cobalt deposition on the hands of workers sharpening hard metal tools (7). A selection of cobalt-containing hard-metal alloys (tungsten carbide bound by cobalt into a hard substance) that were stored in synthetic sweat for 1 week released cobalt in high concentrations, and caused allergic dermatitis in cobalt-sensitized patients (8). Furthermore, cobalt and cobalt salts can be used as pigments and driers in paint, as catalysts, and as additives in fertilizers and animal feed (5, 6). In our view, cobalt allergy and dermatitis remain an occupational challenge, albeit a British survey showed that cobalt allergy accounted for only 4% of 22 184 cases of occupational contact dermatitis (9). This low proportion may be partly explained by difficulties in establishing sources of cobalt exposure.

In 1951, Rostenberg and Perkins emphasized that nickel-plated consumer items were the most important causes of cobalt allergy in dermatitis patients (10). This statement was based on clinical observations at the time, and supported by the co-existence in nature of nickel and cobalt (11). In line with this, cobalt and nickel patch test reactivity are frequently observed together (12). This is likely to be a result of concomitant sensitization rather than cross-reactivity, as indicated by animal and *in vitro* studies (13–15). However, the biological complexity of the co-existence of cobalt and nickel allergy was shown when Hindsén et al. performed oral nickel challenge in nickel-allergic dermatitis patients and found that previous cobalt patch test reactions flared up in some individuals (16). Very little documentation exists about current sources of cobalt exposure. The use of a newly developed cobalt spot test (17) that becomes positive when cobalt ions are released from a metal object showed cobalt release from only a minority of jewellery items and hair clasps in two recent studies (18, 19). It is possible, and even likely, that concomitant exposure to nickel and cobalt from, for example, jewellery was more frequent decades ago than today, owing to increased market prices of cobalt. The present study was aimed at investigating and discussing putative sources of cobalt exposure, and presenting selected epidemiological data on cobalt allergy from patch tested dermatitis patients from Gentofte Hospital in Denmark, in an attempt to better understand cobalt allergy.

Materials and Methods

Exposure part (cobalt spot testing)

Identification

Mobile phones. A large vendor of mobile phones on the Danish market was contacted, and permission to test 50 randomly selected mobile phones currently for sale in Denmark was granted. Cobalt testing was performed by P.J. in the company office. All phones had metallic exteriors, and were selected by P.J. with assistance from a company representative. The company had no production facility in Denmark, and the phones therefore represented a subsample of available devices produced by a given international manufacturer and sold worldwide.

Dental alloys. K.G. contacted four Danish dental laboratories and one Swedish dental laboratory, and asked them to provide samples of cobalt-based alloys used for fixed or removable dental prostheses (Table 1). A total of eight different alloys were made available for analysis. The alloys were tested for cobalt release by J.P.T. at the laboratory at Copenhagen University Hospital, Gentofte.

Orthopaedic implants. At the Department of Orthopaedic surgery, Aarhus University Hospital, revised hip implant components from 52 consecutive patients re-operated on during 2008–2009 were collected and autoclaved. Reasons for revision were aseptic loosening, infection, femur fracture, and component failure. Forty four femoral head, 29 acetabular and 25 femoral components were cobalt spot tested by S.J.

Cobalt Testing

The cobalt test reagent was prepared by mixing 0.1% (wt/wt) oxalic acid, 0.02% (wt/wt) disodium-1-nitroso-2-naphthol-3,6-disulfonate (nitroso R salt) and 5.0% (wt/wt) sodium acetate in deionized water at the Department of Mechanical Engineering, Technical University of Denmark, Lyngby (17). A white cotton stick was dipped in the cobalt test solution, which is a clear yellow solution, and was then rubbed for 20–30 seconds against the test item. A colour change from yellow to red indicated that cobalt ions were released in concentrations that may elicit positive patch test reactions in cobalt-allergic patients (17).

Epidemiological part (cobalt patient characteristics)

Study Population

A total of 19 780 dermatitis patients underwent routine patch testing with the European baseline series at

Table 1. Cobalt–chromium dental alloys provided by different dental laboratories

Dental laboratory	Producer	Co-Cr alloy	Co	Cr	Mo	Si	W	Fe	Mn	Al	C	Co spot test result
Stålet Dental Laboratory, Ballerup, Denmark	Dentaurum, Ispringen, Germany	Remanium GM 800	63.0	30.0	5.0	1.0						+
Tandklinikken i Centrum Tandteknik, Malmö, Sweden	Dr. Henning + Co, Basel, Switzerland	Wironit	64.0	28.7	5.0	*			*		*	+
Tandklinikken i Centrum Tandteknik, Malmö, Sweden	Metoxit AG, Frankfurt am Main, Germany	Gialloy CB Blank	61.0	28.0		1.7	8.5	<0.5	0.25		<0.1	–
Tandklinikken i Centrum Tandteknik, Malmö, Sweden	Heraeus Kulzer GmbH, Hanau, Germany	Heraenium Pw	55.2	24.0		1.0	15.0	4.0	0.8			+
Jaka Dental Laboratory, Frederiksberg, Denmark	Degudent, Germany	CoCr by Compartis	55.2	18.4			18.4	6.0		2.0		+
Esbjerg Dental Laboratory, Esbjerg, Denmark	Dentaurum, Ispringen, Germany	Remanium Secura	58.0	30.0	3.0	1.5	5.5					–
Esbjerg Dental Laboratory, Esbjerg, Denmark	Dentsply	Vitalium 2000	63.6	29	5.3	1.0			*		*	+
Bruun Dental Laboratorium, Rødovre, Denmark	Notatec Plastics & Chemicals Co., Eatontown, USA	Nova-Loy	62.0	30.0	5.5	1.0					0.6	+

Content of metals (%) according to the producer. Results of cobalt spot tests performed in our laboratory.

*Traces of the metal.

Gentofte Hospital between 1 January 1985 and 31 December 2010. The MOAHLFA (Male, Occupation, Atopic dermatitis, Hand eczema, Leg dermatitis, Facial dermatitis, Age above 40 years) index was not routinely registered throughout the study period (20). Thus, MOAHLFA registrations date back to 1994 (2001 for 'Facial dermatitis'), and included 13 461 patients. On the basis of the patient's history concerning dermatitis and exposure, the physician judged whether cobalt allergy was of clinical relevance.

Patch Testing

Testing was performed throughout the study period with Finn Chambers® (8 mm; Epitest Ltd, Oy, Finland) on Scanpor® tape (Norgesplaster A/S, Alpharma, Vennesla, Norway). Cobalt chloride 1% in petrolatum was used throughout the study period. The test concentrations of remaining allergens have been detailed previously (21). Patch test ingredients were from Hermal (Reinbek, Germany), and were applied to the upper back and occluded for 2 days. Readings were performed on day 2, on day 3 or day 4, and on day 7, according to the recommendations of the International Contact Dermatitis Research Group (22). Thus, homogeneous redness and infiltration in the entire test area was scored as a 1+ reaction, homogeneous redness, infiltration and vesicles in the test area were scored as a 2+ reaction, and homogeneous redness, infiltration and coalescing vesicles in the test area were scored as a 3+ reaction. A 1+, 2+ or 3+ reading was interpreted as a positive response. An irritant response, a doubtful (+?) reading or a negative reading was interpreted as a negative response.

Data Analysis

The MOAHLFA index was calculated for the following categories: (i) patch test reactivity to at least one allergen from the baseline series; (ii) patch test reactivity to cobalt chloride; (iii) patch test reactivity to cobalt chloride but not to nickel sulfate (that is, only patients who reacted to cobalt and who did not react to nickel were included); (iv) patch test reactivity to cobalt chloride but not to nickel sulfate and potassium dichromate (that is, only patients who reacted to cobalt but who did not react to nickel or to chromium were included); and (v) patch test reactivity to cobalt chloride only (that is, only patients who reacted to cobalt and who had no other contact allergies to baseline series allergens were included).

Furthermore, the temporal development of patch test reactivity to cobalt chloride across test years was investigated. Here, patch test years were accumulated

so that three consecutive years were presented as one (for example, 1985, 1986 and 1987 were categorized as 1985, and so forth). Also, we evaluated cobalt patch test reactivity in relation to age at patch testing. Finally, we attempted to determine the proportion of positive patch test reactions that had been recorded as being of clinical relevance during the period 2000–2010. All data analyses were performed with SPSS (SPSS Inc., Chicago, IL, USA) for Windows™ (release 15.0).

Results

Exposure part (cobalt spot testing)

Mobile phones. Investigation of 50 mobile phones showed no positive cobalt spot test reactions.

Dental alloys. Cobalt testing showed that six of eight alloys were cobalt spot test-positive (Table 1).

Orthopaedic implants. Of 98 tested hip implant components, 10 (10.2%) gave positive cobalt spot test reactions. Cobalt release was primarily observed from femoral head components and femoral components, but not from acetabular components.

Epidemiological part (cobalt patient characteristics)

A total of 19 780 dermatitis patients (64.6% women and 35.4% men) aged 4–99 years at the time of patch testing were tested with 1% cobalt chloride between 1985 and 2010. The MOAHLFA index scores of 13 461 patients tested between 1994 and 2010 are shown in

Table 2, and suggest that cobalt allergy was mainly observed in female patients, and that the sex association was weakened in patients with patch test reactivity to cobalt (but without co-reactivity to nickel and chromium) and to cobalt alone. Also, it appeared that isolated patch test reactivity to cobalt was less associated with occupational dermatitis and hand eczema than patch test reactivity to cobalt in combination with other contact allergies. We evaluated the proportions of concomitant contact allergy to other chemicals and metals in cobalt-allergic patients. Allergy to the following substances was frequently observed together with cobalt: nickel (54.6%), chromium (22.1%), fragrance mix I (12.9%), fragrance mix II (9.5%), *Myroxylon pereirae* (8.9%), and thiuram mix (8.7%). To determine whether the proportion of concomitant reactivity in cobalt-allergic patients differed from the proportion in patients with other contact allergies, colophonium 20% pet. was used as a reference contact allergen. Colophonium was chosen because the overall prevalences of cobalt allergy and colophonium allergy were identical (4.1%). Among colophonium-allergic patients, the concomitant reactivity to most allergens was nearly identical to the concomitant reactivity observed in cobalt-allergic patients (data not shown). Thus, cobalt chloride seemed not to be overrepresented as a concomitant contact allergen when compared with other baseline series allergens.

Patch test reactivity to cobalt followed the temporal development of patch test reactivity to nickel to some degree, whereas the prevalence of cobalt patch test reactivity without concomitant nickel reactivity and the prevalence of isolated cobalt reactivity seemed to be fairly stable over time (Fig. 1). The prevalence of cobalt allergy was higher in middle-aged female patients (as

Table 2. MOAHLFA index* in 13 461 dermatitis patients aged 4–99 years who were patch tested at Gentofte Hospital during 1994–2010

Frequency of variables	All patients (n = 13 641), % (n)	Cobalt-allergic patients (n = 568), % (n)	Cobalt-allergic patients without nickel allergy (n = 247), % (n)	Cobalt-allergic patients without nickel and chromium allergy (n = 178), % (n)	Patients with isolated cobalt allergy (n = 89), % (n)
Males	34.8 (4753)	19.7 (112)	35.5 (88)	33.7 (60)	37.1 (33)
Occupational dermatitis	14.2 (1940)	18.8 (107)	15.0 (37)	12.4 (22)	10.1 (9)
Atopic dermatitis	13.7 (1875)	15.8 (90)	17.0 (42)	20.2 (36)	19.1 (17)
Hand dermatitis	33.3 (4548)	52.1 (296)	48.6 (120)	47.8 (85)	42.7 (38)
Leg ulcers	8.1 (1102)	4.9 (28)	6.5 (16)	6.2 (11)	7.9 (7)
Facial dermatitis†	21.2 (1646)	20.4 (74)	20.9 (32)	25.5 (26)	22.7 (10)
Age >40 years	66.0 (9000)	61.4 (349)	76.5 (189)	75.8 (135)	70.8 (63)

Facial dermatitis was only registered from 2001.

*The MOAHLFA index stands for Male, Occupational dermatitis, Atopic dermatitis, Hand dermatitis, Leg ulcers, Facial dermatitis, and Age above 40 years. It shows the characteristics of patients tested at a patch test clinic and may be used for comparison (23).

†For the period 2001–2010; all patients, $n_{\text{total}} = 7761$; cobalt-allergic patients, $n_{\text{total}} = 363$; cobalt-allergic patients without nickel allergy, $n_{\text{total}} = 153$; cobalt-allergic patients without concomitant nickel–chromium allergy, $n_{\text{total}} = 102$; patients with isolated cobalt allergy, $n_{\text{total}} = 44$.

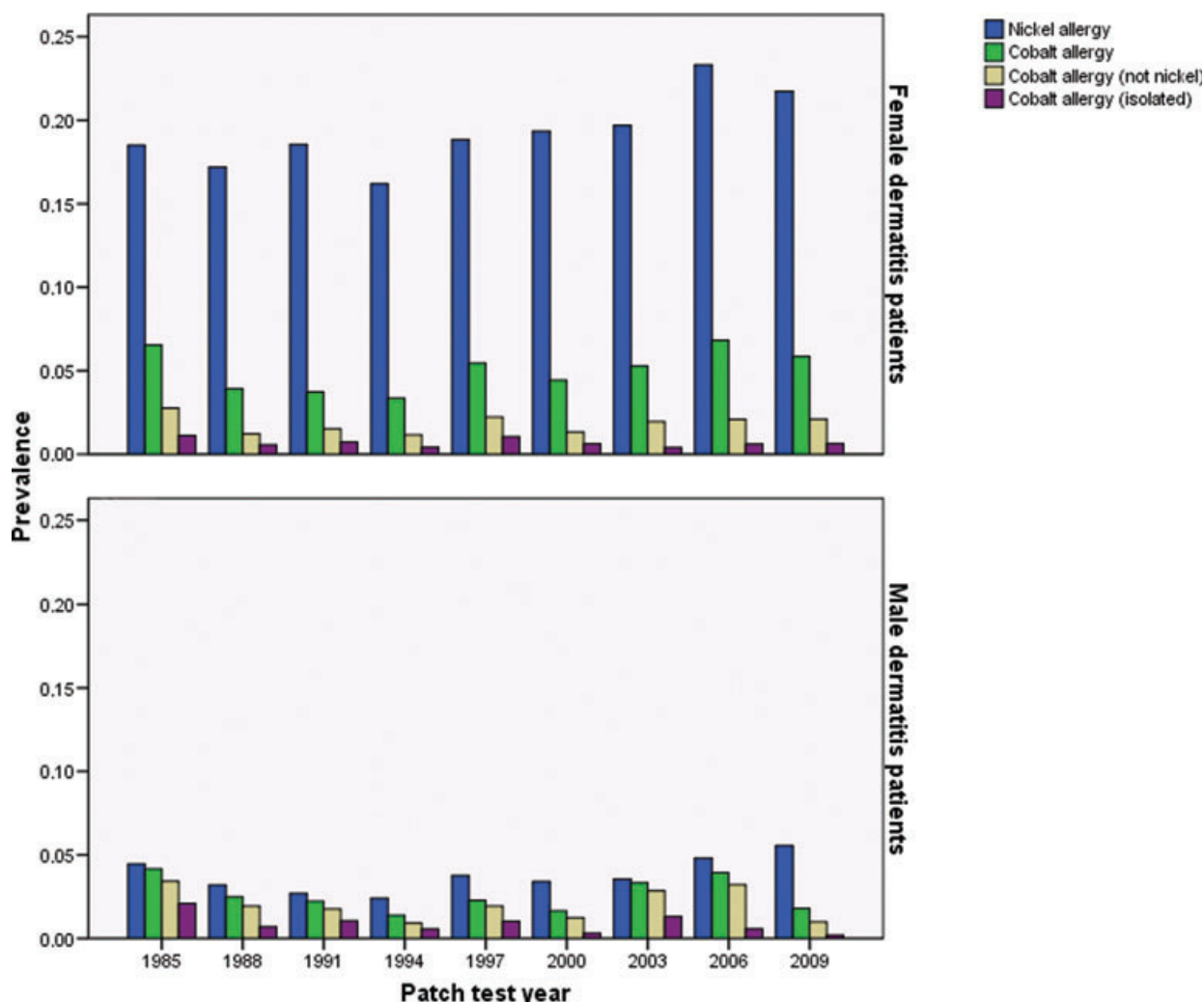


Fig. 1. The frequency of nickel and cobalt allergy in patch-tested dermatitis patients in Gentofte ($n = 19\,780$), over time (1985–2010) by intervals. Prevalence estimates on the vertical axes are presented as decimals ranging from 0 to 1. Hence, 0.1 equals 10%.

observed for nickel allergy), whereas patch test reactivity to cobalt in male patients and both patch test reactivity to cobalt without concomitant nickel reactivity and patch test reactivity to isolated cobalt in female patients seemed not to be associated with any specific age group (Fig. 2).

The mean proportion of positive patch test reactions to baseline series allergens that were judged to be of clinical relevance between 2000 and 2010 was 43.9%. These proportions were 39.9% for nickel patch test reactivity, 27.2% for cobalt patch test reactivity, 22.9% for cobalt reactivity without concomitant nickel reactivity, and 25.5% for isolated cobalt reactivity. Only epoxy resin had a lower prevalence (25.8%) of clinical relevance than cobalt.

Discussion

The present study confirms that cobalt is a difficult allergen to test, in the sense that it may be difficult to determine the clinical relevance of positive patch test reactions. Also, it is difficult to be certain that a positive patch test reaction to cobalt really does indicate a genuine allergy, as false-positive results are common with the patch test concentration used. Hence, in our database, only 1 in 4 patients with cobalt allergy was judged to have a clinically relevant reaction. This is a clinical challenge worth debating, as the prevalence of cobalt allergy is relatively high (6). As putative sources of cobalt exposure have been scarcely investigated, it is considered that clinicians generally lack sufficient knowledge for thorough judgement and decision

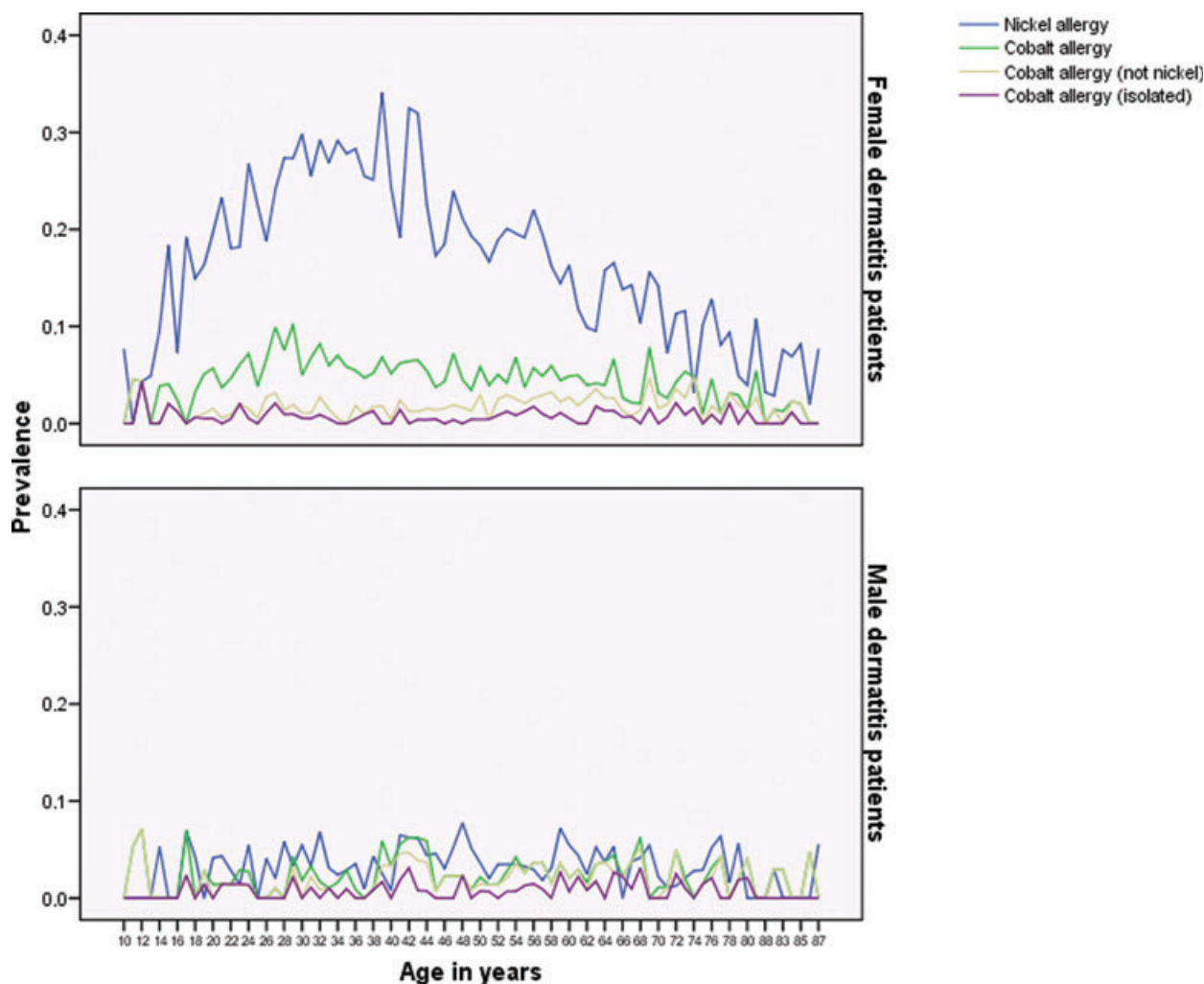


Fig. 2. The prevalence of cobalt allergy stratified by age, that is, age in years when contact allergy to cobalt was diagnosed. Patients aged <10 years and >89 years were low in number, and were hence excluded to prevent visual disturbance of outliers ($n_{\text{total}} = 19\,611$ patients). The prevalence of nickel allergy and cobalt allergy is highest in young to middle-aged female dermatitis patients, whereas no peaks can be observed for isolated cobalt allergy. Prevalence estimates on the vertical axes are presented as decimals ranging from 0 to 1. Hence, 0.1 equals 10%.

making when interpreting positive cobalt patch test reactions. By developing a cobalt spot test and using it to investigate cobalt release from various sources of exposure, we hoped to identify and quantify sources. However, we have so far shown that cobalt release is infrequently encountered from jewellery, hair clasps, and non-professional work tools (17–19), which are all items that our patients are frequently exposed to. No cobalt release was identified from mobile phones in this study (Table 3). However, it should be emphasized that cobalt release from jewellery can be clinically relevant, as illustrated by a Swedish case report showing allergic cobalt dermatitis caused by a necklace (24). In recent reports, cobalt was released

particularly from dark or black-coloured jewellery (18, 19). Cobalt is also used in gold alloys and gold platings for jewellery (25). Cobalt may thus be found in cheap as well as expensive jewellery of different colour. Further exposure studies on items that may be in repeated or prolonged skin contact are clearly needed to reproduce these findings and to identify other sources of cobalt exposure. Despite the absence of cobalt release from the investigated consumer items, cobalt may previously have been released from such items together with nickel, thereby maintaining the high frequency of cobalt allergy. In support of this notion, patch test reactivity to cobalt seems to follow the temporal development of nickel patch test reactivity

Table 3. Various items that have been investigated for cobalt release with the newly developed cobalt spot test

Object	Number tested	Positive for cobalt release, % (n)
Cobalt-based dental alloys, Copenhagen	8	75 (6)
Orthopaedic implants, Copenhagen	98	10.2 (10)
Jewellery, Copenhagen (19)	237	1.7 (4)
Earrings, China and Thailand (18)	557	0.007 (4)
Hair clasps, Copenhagen (19)	117	0
Work tools, Copenhagen	200	0
Mobile phones, Copenhagen	50	0

in female dermatitis patients (Fig. 2). Furthermore, cobalt allergy, just like nickel allergy, was, as expected, much more common in female patients, as women are more often pierced and tend to wear more jewellery than men (Fig. 1) (3). Other sources of consumer cobalt exposure have previously been suggested. A Finnish study showed that 25% of 49 eye shadows contained less than 1 ppm cobalt, but also that some eye shadows contained up to 41 ppm cobalt (26). In Spain, 78% of the 30 most popular domestic detergents and cleaners sold in 1985 contained cobalt (27). Also, Wahlberg et al. showed that three of eight detergents contained cobalt (28). Scattered case reports have shown exposure to cobalt resulting in clinical disease, for example from green plastic shoes and glitter colour lacquered on nails (29, 30). Finally, it should be noted that polishing and surface coatings in consumer metal items that have been investigated may have prevented cobalt release. Hence, if used items had been tested, a higher proportion of cobalt release may have been found. The cobalt spot test is useful for screening purposes, but cannot replace the chemical analysis of materials.

This study convincingly shows that cobalt ions are released from a considerable proportion of orthopaedic implants and dental alloys. Thus, more than half of the assessed cobalt-based dental alloys and 10% of removed hip implant components gave positive cobalt spot test reactions. Cobalt ions can be released from orthopaedic implants as a result of wear and corrosion, and will rapidly reach the immune cells in the surrounding tissues, blood, kidney, and liver, and cause sensitization (31). A linear correlation was found between serum metal ion levels following insertion of implants and lymphocyte reactivity in patients as compared with controls (32). Also, epidemiological studies have shown that subjects may develop metal allergy following joint replacement, albeit infrequently (33, 34). Perhaps cobalt sensitization from

orthopaedic implants and other sources may explain a proportion of the positive cobalt patch test reactions in dermatitis patients, especially in cases where clinical relevance is undetermined and where the clinician has neglected to consider such systemic exposures. However, it should be underscored that the cobalt spot test was developed for the purpose of testing items in prolonged skin contact and not for testing orthopaedic alloys; hence other, and probably lower, cobalt release concentrations may be relevant. To what degree intraoral exposure to cobalt-containing dental alloys may result in cobalt ion release and contribute to positive cobalt patch test reactions in our patch test populations is also difficult to determine. Cobalt-based alloys are frequently used for fixed partial denture or removable prostheses, and could therefore sensitize a large proportion of, especially, older patients. On the other hand, some patients might develop tolerance to cobalt following primary intraoral cobalt exposure, as shown for nickel (35). We propose that cobalt release from implants should be considered as a cause of sensitization in our patients. Cobalt-based dental and jewellery alloys may also cause sensitization and dermatitis in dental technicians and jewellers who handle the materials extensively. Other sources of mainly occupational exposure to cobalt, such as cement, clay, putty, pigments, and drying agents in paints (6), should not be forgotten, although the present study focused on metallic items. Apart from assessing cobalt release from items in artificial sweat and by the cobalt spot test, assessment of cobalt on the skin surface is considered to be important for identifying the risks and causes of cobalt dermatitis. Acid wipe sampling is a new method with high sampling efficiency (>90%) for the assessment of nickel, chromium and cobalt deposited on the skin. The method has been used in occupational, experimental and clinical studies (7, 36, 37).

It has been debated over the years whether weak cobalt reactivity (1+) can be a marker of general immune reactivity, as weak cobalt patch test reactivity can be difficult to replicate (38). Negative lymphocyte transformation was found in 6 patients with weak test reactions, whereas positive lymphocyte transformation was found in 8 patients with definite positive reactions (39). Fischer and Rystedt retested cobalt-allergic patients over a 6-month period and found that 7 (100%) of 7 patients with 3+ reactions still reacted, that 22 (73.3%) of 30 patients with 2+ reactions still reacted and finally that only 3 (17.6%) of 17 + reactions were retrieved (40). On the basis of history, retesting, and serial dilution testing, they found that only 62.9% of the initial positive reactions were truly allergic (40). Katsauro et al. studied 180 cement workers with contact dermatitis, 98 of whom had positive patch

test reactions to cobalt (41). The workers were retested after 2–6 years, and cobalt allergy persisted in only 47%. Other studies have evaluated the relevance of positive cobalt test reactions. Thus, de Fine Olivarius and Menné showed that only 11 of 19 patients with positive patch test reactions to 1% cobalt chloride reacted to 100% metallic cobalt discs (42). They concluded that the value of testing with cobalt chloride is limited by a high frequency of irritant and questionable reactions. Cobalt chloride 0.5% pet. has, since the late 1980s, been used in Sweden for routine patch testing, to reduce the risk of irritant and questionable reactions (6), an approach that should be considered elsewhere. Nielsen et al. found it difficult to elicit allergic cobalt dermatitis on the hands in cobalt-allergic patients, whereas nickel-allergic patients more easily developed allergic nickel dermatitis on the hands in an experimental setting (43, 44). Hegewald et al. recently showed that the frequency of irritant, doubtful and weak allergic reactions to cobalt chloride increased during cold and arid weather, whereas strong allergic reactions did not depend on weather conditions (45). Storrs and White showed that 32% of 222 patients had irritant reactions to cobalt, and that these reactions were poral and seemed to reflect a toxic effect of cobalt on the acrosyngium (46). The above findings may explain why we identified clinical relevance of positive cobalt reactions in only 1 of 4 patients. However, it should be noted that determining the clinical relevance of positive patch test reactions is often difficult; especially for cobalt, as there has not, until recently, been access to a spot test, and knowledge on use and exposure is limited. A recent study might support the idea that increased immune reactivity in some cases can result in cobalt patch reactivity (47). Thus, patch test data from patients with primary cutaneous lymphoproliferative disorders other than mycosis fungoides were compared to patch test data from consecutive dermatitis patients. As the only contact allergy, cobalt reactivity was significantly more often observed in these patients than in controls, perhaps indicating immune reactivity, although a causal relationship was not established. In the present study, we could not support the idea that cobalt chloride reactivity was overrepresented as a concomitant contact allergen when compared with colophonium.

Isolated cobalt allergy is of particular interest to study, as nickel may strongly influence the epidemiology of cobalt allergy. We found a stable rate of isolated cobalt allergy over the study period (Fig. 1) and across age groups (Fig. 2). In Odense, Denmark, a recent patch test study found a decreasing prevalence of isolated cobalt allergy among young female dermatitis patients between 1992 and 2009, and an increase in older patients (48). In Gentofte, Denmark, an increase in isolated cobalt allergy was also observed in female dermatitis patients aged >50 years between 1985 and 2007 (12). In our study, isolated cobalt allergy seemed to be less associated with being female, hand eczema and occupational dermatitis than cobalt having allergy (Table 2). These observations contrast non-isolated with findings from the 1940s and 1950s, where isolated patch test reactivity to cobalt was associated with occupational exposure, as it was often seen in pottery and metal workers (49, 50). A Swedish study including 4034 dermatitis patients found isolated cobalt allergy (i.e. no simultaneous reaction to nickel or chromium) in both sexes and most age groups (38). This is in accordance with our findings (Fig. 2). However, Hegewald et al. showed that isolated cobalt allergy was significantly associated with young age (51). Also, they found that the chance of being allergic to other contact allergens was elevated in patients with cobalt allergy (51). This could not be confirmed in our study. Ruff and Belsito found that isolated cobalt allergy was associated with dermatitis on the lips (52). We found no association between facial dermatitis and being cobalt-allergic in general or having isolated cobalt allergy when using dermatitis patients as a control group (Table 2).

In summary, the epidemiology of isolated cobalt allergy is not uniform, and seems to have changed over the years, from being mainly associated with occupational exposure to being equally represented in men and women and across age groups. Questionnaire studies might be helpful to better characterize this group of dermatitis patients. Systematic assessments of cobalt release from consumer items and in work environments, together with skin exposure assessments of cobalt, will increase our knowledge about cobalt exposure and dermatitis. One should consider the use of lower test concentrations to decrease the proportion of test reactions without clinical relevance.

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