

Review Article

Contact allergy to gold as a model for clinical-experimental research

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The high frequency of contact allergy to gold in patients with dermatitis was established after exhaustive skin testing, determining the right test agent, the best concentration, and repeated test readings. Metallic gold in contact with skin is slowly ionized, permitting absorption and haptensisation. Contact allergy to gold is statistically correlated to the presence of dental gold. But in many case reports it has also been attributed to wearing gold jewellery, albeit not statistically demonstrated. Epicutaneous testing with gold salts increases the blood gold level, and by intramuscular injection systemic contact dermatitis is provoked in an allergic individual. In coronary heart disease, gold-coated intravascular stents have been shown to be correlated to contact allergy and even to an increased risk of restenosis. Gold is far from inert.

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Contact allergy to gold and contact dermatitis from this metal are not recent findings. Several papers with case reports on patch test-proven dermatitis from metallic gold mainly caused by jewellery, but also other items in close contact with the skin or mucous membranes have been published (1). In the early nineties, in search for a more effective test agent in the dental series than those hitherto used, we added gold sodium thiosulfate (GSTS) routinely to the dental as well as to the baseline series and found a fair amount of positive patch tests in the dental series with relevance. However, to our surprise there was also a high frequency of positive patch tests to GSTS (0.5% pet.) when testing patients with a suspected contact dermatitis (2). The frequency of 8–9% aroused suspicions of false positive test reactions but comprehensive investigation using several methods demonstrated a true contact allergy (2, 3). During subsequent years, similar figures for GSTS allergy were observed in other clinics worldwide.

Test Technique

Why was this frequent contact allergen among dermatitis patients so late to be discovered? An important reason was probably the myth of gold as

being an inert metal not releasing allergenic material, and a further reason was using unsuitable test techniques: wrong test agent, wrong concentration, and wrong timing. Metallic gold has been found unsatisfactory, usually yielding false negative results. Gold trichloride was used by Kligman (4) in a human maximisation test and found to be clearly allergenic. It has, however, irritating properties; this does not seem surprising as hydrochloric acid is formed by GSTS dissolved in water. As an allergen, gold trichloride is also much weaker than GSTS (5). GSTS can easily be increased in test concentration from 0.5% to 2.0% in pet., and even to 5.0% and 10.0%, without inducing irritant reactions (6).

During the last decade we have routinely used GSTS 2.0% pet in the baseline series and the level of positive test reactions has been fairly stable; in the year 2008 it was 13.8% (90/651) and of those 71/90 (78.9%) were females.

Using serial aqueous dilutions in 35 patients with contact allergy to GSTS, there was a varying strength of reaction with a positive test threshold from 5.0% down to 0.016%, the most frequent end point being 0.5% (7). The prevalence of gold allergy in the healthy population is not known but was found to be 4.8%–12.5% in four 'control

groups' without skin disease, when patch testing with 0.5% pet. (8–11).

It was soon found that patch test reactions to GSTS, albeit of the expected crescendo type, were often delayed, even so that a negative reaction on day(D) 3 changed to a positive one on D7, a phenomenon similar to that observed with other allergens such as neomycin and corticosteroids. In a prolonged study (12), it was found that patch test reactions could develop even later than D7 without being caused by active sensitisation. In 5 of the 10 meticulously followed patients, the contact allergy would have been missed if the tests had been read on D3 only. So from this and other reasons, most dermatologists nowadays recommend – and routinely perform – at least two readings, preferably on D3 and D7. Occasionally, positive patch tests to GSTS may become longstanding, for weeks and even months, and gradually develop a nodular appearance characterised by an intense lymphocytic infiltrate without epidermal involvement (13, 14).

Prerequisites for the elicitation of an allergic contact dermatitis from metallic gold, of course, are the ionisation of the 'inert' metal, release and then skin penetration. Metallic gold is not released into artificial sweat and other simple salt solutions (15, 16), but is soluble in a wide range of aqueous amino acid solutions (17, 18) with a similarity to real human sweat. Gold from metallic alloys is released and dissolved into the saliva (19), and there is a correlation between dental gold and the gold level in blood (20, 21).

Obviously, metallic gold in contact with skin or mucous membranes may be dissolved and ionised in biological media and further absorbed into the circulation. This provides the background for a 'systemic allergic dermatitis' (see below), occurring after topical exposure to an allergen and resulting in a distant skin reaction (1,22). Furthermore, contact allergy to gold is correlated to the presence of dental gold (23–27), but there are only a few distant skin reactions reported supposedly caused by dental gold (25–28).

Lesson: A negative test may be false; try other agents or techniques! A D3 reading only cannot be considered *lege artis*.

Relevance

While contact allergy to GSTS is observed frequently in clinical material, a resulting allergic contact dermatitis to gold is much less common. Requirements for a clinical relevance should include a positive skin test, a recent exposure to the allergen, and a reasonable connection to the patient's dermatitis (29). With metallic gold as the suspected

allergen, there is the special problem of exposure: almost everybody, females in particular, has had close skin contact, at some time, with gold jewellery, which prevents statistical comparisons. Another problem is the slow development of clinical dermatitis induced by e.g. jewellery – several days according to many patients – just as with the late development of GSTS test reactions. This could be explained by the slow release of ionised gold from the metal.

The frequency of a clinical relevance in patients with a GSTS allergy varies considerably according to the literature. This in turn may be a result of the method used when interviewing. Routinely, the patient is questioned with the positive allergen known by the dermatologist and presented to the patient, i.e. in a heavily biased situation in which the patient is 'pressed' to recall hypersensitivity to a particular allergen. This leads naturally to a high degree of clinical relevance. To diminish bias, we gave the patients a questionnaire *before* the patch test, which probably contributed to the low grade of relevance (23). Sabroe et al. (30), who also used a questionnaire before patch testing, found a clinical relevance in half of their patients allergic to gold. As mentioned above, contact allergy to GSTS is statistically correlated to the presence of dental gold (Fig. 1). In addition, conclusions could be drawn by recording the eczema sites in our patients with gold allergy by which we found an over-representation of fingers and ears, suggesting a correlation to causative jewellery (Fig. 2). Metallic gold could also be shown to provoke experimental as well as iatrogenic gold dermatitis (1, 31) and clinically, gold allergy could be correlated to pierced earlobes (30, 32). Finally, several occupational sources of exposure to metallic or ionised gold are known (33), but sensitisations in workplaces seem to be infrequent.



Fig. 1. Contact stomatitis and gold allergy.



Fig. 2. A seven-year old girl with a pierced earlobe, contact dermatitis, and gold (not nickel) allergy.

Lesson: Ubiquitous exposure prevents establishment of relevance; bias should be minimised when interviewing patch-tested patients; alternatively, causative factors may be identified by indirect measures in large materials; metallic gold can be ionised in biological media to form haptens.

Systemic Allergic Dermatitis

A more or less widespread dermatitis, believed to be induced by a temporarily circulating contact allergen, is named systemic allergic dermatitis (SAD), previously also called 'endogenous contact eczema' (34). This has been the subject of several reports during the last half-century and also some reviews (35, 36). Controlled studies started in the 1970s with orally administered allergens, mainly salts of nickel, chromium, and cobalt contained in capsules (37–39), documenting the clinical patterns as well as dose-response conditions. One drawback with the oral provocation was a certain delay of clinical reactions in addition to a probable metabolism and/or conjugation of the chemical during gastrointestinal digestion and absorption. With gold, these problems could be diminished, as gold salts for many years have been given by intramuscular injection for treating rheumatic patients, usually as gold sodium thiomalate (GSTM). With our experience of cross-sensitivity between the two monovalent salts (3), GSTM could be chosen as the circulating allergen and be deposited almost directly in the blood circulation. Furthermore, we found that a dose of 10 mg, a fifth of the usual therapeutic dose, was quite sufficient to evoke the different allergic reactions of SAD (40).

The clinical signs of experimental SAD were fairly uniform in controlled studies (7). Thus, in 35 patients with contact allergy to gold i.m. provocation with GSTM induced a flare-up of previously



Fig. 3. Flare up of a previous allergic contact dermatitis from a golden necklace as expression of systemic allergic dermatitis provoked by an i.m. injection of gold sodium thiomalate.

positive patch tests with GSTS in 80%, of a previous contact dermatitis in 26% (Fig. 3), of toxicoderma in 46%, and of fever in 60%. In other studies, a high frequency of palmar hand eczema (pompholyx) as an expression of SAD has been reported for some allergens, such as nickel (41) and sesquiterpene lactones (42).

Healed patch tests could be up to 2 years old but were, nevertheless, activated after intramuscular provocation and also old intradermal tests were activated. Oral nickel provocation has shown specificity against placebo, against healed irritant reactions, and against tuberculin reactions (43). With i.m. gold provocation there was a high-sensitivity/low-eliciting dose and a specificity against placebo (7). Also, the cross-sensitivity between GSTS and GSTM was confirmed in this experimental model.

The tissue dynamics of well healed but now flaring positive patch tests after a single GSTM provocation were dramatically shown by laser Doppler imaging (44). An increased blood flow in the activated patch tests was recorded 2 hours after the i.m. injection with a peak around 6 hours, subsiding at 72 hours. In the GSTS dilution steps, the increased blood flow was observed earliest at the strongest test concentrations. On the other hand, some low GSTS concentrations, which at the previous patch test had been negative, now showed an increased blood flow. This agrees with clinical findings in patients provoked with gold (40) and with nickel (45). Thus, the 'invisible allergy' of Kligman (46, 47) was now confirmed also in controlled studies; see Table 1 for methods to show false negatives.

Concomitantly with the increased blood flow in the flaring patch tests after systemic GSTM provocation, there was a marked release in the circulating blood of acute-phase reactants and inflammatory cytokines (48). By a crossover experimental design,

Table 1. Positive patch test to GSTS means contact allergy

Gold allergy established	Reference
Patch test with GSTS 0.5% pet	2
Patch test with GSTS dilution series	2
Patch test with other gold salts	2
Intracutaneous test with GSTS and GSTM	2, 3
Histology, immunohistochemistry	14
Gold allergy confirmed	
SAD blinded versus placebo	40
SAD specific versus nickel	49
Cytokine release versus nickel	49
SAD after topical application	1

GSTS, gold sodium thiosulfate; GSTM, gold sodium thiomalate; SAD, systemic allergic dermatitis.

including gold and nickel provocation (49), the resulting cytokine release was shown to be allergen specific. There was a significant increase of TNF- α , TNF-R1, IL-1RA, and neutrophil gelatinase - associated lipocalin after gold stimulation, but an increase of just TNF-R1 after nickel provocation. Apparently, the cytokines released were involved in the immunological reaction, but if they implied cause or effect of the flare-up could not be decided.

The pathogenesis of SAD has been repeatedly investigated and discussed with e.g. evidence and speculation on circulating metal-immune complexes as instrumental (36, 50) or concerning the cellular mechanisms (51). With regard to gold, a positive patch test to GSTS compared to a healed but later flaring test reaction showed clinical as well as morphological differences. In a blind study, initially positive reactions to gold and to nickel could not be differentiated, either on clinical or on histopathological grounds, and showed a classical pattern for contact allergy (14). The flaring patch test was in principle similar, but in many cases more extensive and oedematous (52). Before systemic provocation, the priming as a result of the initial patch test was evidenced immunohistochemically by sparse perivascular UCHL-1 stained memory T-cells in papillary dermis as well as by endothelial ELAM-1 staining. During flare-up, there were larger and more extensive lymphocytic foci, an ELAM-1+ endothelium as well as lymphocytic epidermotropism. Also, probably instrumental in the flare-up was an accumulation of mastcells and blood-borne monocytes/macrophages which might explain the oedematous character of the flaring test reactions. Thus, signs of priming and the presence of a persistent 'local memory' were present before systemic provocation, thereafter markedly strengthening in degree and quality.

Lesson: The model implies rapid blood contact of the allergen; old patch and intradermal tests

are activated; it provides a sensitive method for weak allergy, even 'invisible allergy'; implies an additional method of showing allergen specificity and cross-sensitivity; micromorphological differences between primary patch tests and reactivated tests are obvious; dynamics are visualized by laser Doppler imaging and biochemically by cytokine release, even this allergen specific.

Metallic Gold as Implants

Metallic stents inserted into coronary vessels for maintaining blood flow after ballooning have usually been made of stainless steel. During the 1990s, stainless steel stents with a thin coat of a gold alloy ('gold stent') became popular, mainly to improve visualisation of the X-ray image of the stent during implantation and follow-up (Fig. 4). However, suspicions arose of side effects such as allergic reactions to metallic alloys (53). A pilot study (54), confirmed by a large controlled study (27), showed that patients with an intracoronary gold stent had a higher frequency of contact allergy to gold than patients stented with stainless steel only. It was also found that patients with a gold stent had a high gold level in blood, and the higher the blood gold level, the stronger was the intensity of the gold allergy (55).

A coronary vessel treated with a metallic stent can become re-occluded; retrospectively, it was found that such restenosis occurred more frequently



Fig. 4. Intravascular stainless steel stents, the lower one (gold-coated) is deflated.

in patients having obtained a gold stent than in those with a regular stent of stainless steel only. This complication was three times more frequent in patients with a concomitant gold allergy (56, 57). An increased risk of restenosis also in the renal arteries has been observed in patients with gold-coated stents (58). At present, gold stents are only rarely used and new stent materials are continuously being tested.

How to explain the statistical correlation between the presence of a gold stent and contact allergy to the metal? There is obviously a need for a prospective study to clarify if the patients were allergic to gold before heart surgery or became so following the intervention. Most patients, however, were operated upon as emergency cases, so there was no time for an allergological investigation. This logistical problem was solved for a study on extremity fractures and nickel allergy (59); patch testing was performed 1–2 days after orthopaedic surgery, i.e. before any new sensitisation had had time to develop. In our retrospective studies (27, 56), statistics and circumstantial evidence speak in favour of our patients having been sensitized by the stent itself. Also, Langerhans cells and other factors required for a sensitisation process have been demonstrated in the vessel intima (60). Additionally, gold stents, gold allergy, and dental gold are associated in our patients with heart disease. Previous periodontitis (and following dental restoration with gold?) has been suggested as leading to chronic heart disease (61, 62), which should imply that the sensitisation might have had occurred by way of a dental restoration with gold. Dental gold was observed in many of our stented patients (27).

Today, dental gold is frequently used but with great variations in different countries, apparently based on socio-economic conditions. In Sweden, probably one-third of the adult population have dental gold with few clinical consequences aside from findings reported above.

In clinical material of patients patch-tested because of complaints within the oral cavity, the frequency of gold allergy is much higher than in patients tested because of a suspicion of an allergic contact dermatitis. Thus, from our clinic in 2008, there were 24.1% versus 13.8%, respectively, test positives to GSTS. This agrees with findings of different inflammatory conditions of the oral mucous membrane with a causal connection to gold allergy (63–65). An interesting case of 'systemic allergic stomatitis' was described where the background was oral lichenoid reactions, dental gold, and gold allergy (66). When the patient was later given a coronary gold-coated stent, there was a vesicular flare-up of the oral disease, which also

was reactivated when the dental gold was removed. However, in spite of several reports on a causal relationship between contact allergy to gold and oral lichen lesions, a recent controlled study could not confirm such an association (67).

Gold implants have been used for substituting a lost eye. The earliest report of a test-proven contact allergy to gold was an extensive contact dermatitis elicited by a gold-ball orbital implant (68). Patients with a facial nerve injury and inability to close the eyelids have been lid-loaded with a gold weight permitting closure; some have, however, acquired an allergic contact dermatitis requiring removal of the weight (31).

Lesson: Gold-coated coronary stents are correlated to an increased frequency of contact allergy to gold and even an increased frequency of restenosis of the vessel. Is the vessel intima another tissue in which sensitisation and/or elicitation of a contact allergy may occur? Also, the orbital cavity and the eyelid may be the starting-point of an allergic contact dermatitis from metallic gold.

Effects of Circulating Gold

Gold salts have been widely used for treating rheumatologic diseases but also others such as bullous dermatoses and even tuberculosis. The drugs have been given mainly intramuscularly (e.g. GSTM) and orally (e.g. auranofin) with good results, but also many side effects (69). The half-life of injected GSTM has been given as 6 days, and elimination 10–35 days (70). Circulating gold is mainly bound to albumin; it is taken up and stored preferentially in parenchymatous organs but also in skin, particularly in dermis (71).

For the monovalent salt GSTM, a topical application with simple occlusion is sufficient to increase the blood gold level 10 times over baseline (72). It now also seems established that gold is released and ionised from metallic gold and absorbed through the skin (1) as well as from mucous membranes (19, 20). These processes lead to a demonstrable gold level in circulating blood, and in many cases to a contact allergy to gold with clinical consequences which, as far as we know, are mainly of dermatological character. With regard to dental gold, an immediate rise of blood gold level after gold insertion was recorded as stable over time, at least up to 15 years (21); obviously, gold is released continuously from the dental alloy.

Interestingly, blood gold level was found to be correlated to the patch test intensity, i.e. the higher the blood gold level the stronger the test reactivity (55). This was confirmed in a study with topical provocation of GSTS (73), showing that the level of blood gold level influences the patch test

intensity. Should this scenario be demonstrated also for other allergens, it should imply a new pathogenic principle in contact allergy.

Lesson: Gold is continuously released from dental and intravascular gold implants, leading to a sustained level of gold in the circulation; circulating gold may influence the patch test reactivity to the same allergen. Even an occlusive patch test with GSTS markedly raises the blood gold level; how many other haptens appear in the circulation following a standard patch test?

Concluding Remarks

The standard patch test is still the most reliable tool for demonstrating contact allergy. Although the present review describes the various methods to confirm contact allergy to gold, false negative tests also do occur. Generally speaking, dermatologists are constantly on the alert to false positives but perhaps less keen on demonstrating the false negatives. By continuously improving the technique, the test agent, and the reading, a new allergen is occasionally discovered, and even an old metal such as gold might earn the title of 'allergen of the year' (74).

Gold is far from inert! From jewellery and other applications to the skin as well as by dental or vascular implants it may induce contact allergy, which in the long run may lead to contact dermatitis, contact stomatitis, or vasculitis with restenosis, respectively. Generally, however, the clinical consequences are few and limited.

Gold certainly causes delayed allergy, the reactions appearing and subsiding slowly. Gold is a model agent for experimental studies on SAD, yielding information on clinical patterns, micromorphology, dynamics, and biochemistry of the flare-up of endogenous contact dermatitis. Now that gold in blood has been shown to influence the intensity of gold patch tests, the fate and effect of a circulating contact allergen await further research.

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