Gold concentration in blood in relation to the number of gold restorations and contact allergy to gold

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Ahnlide I, Ahlgren C, Björkner B, Bruze M, Lundh T, Möller H, Nilner K, Schütz A. Gold concentration in blood in relation to the number of gold restorations and contact allergy to gold. Acta Odontol Scand 2002;60:301–305. Oslo. ISSN 0001-6357.

Previous studies have demonstrated an association between gold allergy and the presence of dental gold restorations. The aim of the present study was to investigate the relationship between the concentration of gold in blood (B-Au) and the number of tooth surfaces with gold alloys in subjects with and without contact allergy to gold. In 80 patients referred for patch testing because of eczematous disease, blood samples were taken and analyzed for B-Au using inductively coupled plasma mass spectrometry. The detection limit for the Au determination was 0.04 μg/L. In addition, a dentist made a clinical and radiological examination of the patients and registered the number of dental gold surfaces. Patients with dental gold restorations had a statistically significantly higher B-Au in Mann-Whitney U test ($P = 0.025$), (range <0.04–1.07 μg/L) than patients without (range <0.04–0.15 μg/L). Furthermore, a positive correlation was found between B-Au and the number of dental gold surfaces ($P < 0.01$). There was no statistically significant difference in B-Au between persons with and without contact allergy to gold. The study thus indicates that gold is released from dental restorations and taken up into the circulation. □ *Contact allergy; corrosion; dental cast restoration; gold allergy; gold release; patch test*

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When gold sodium thiosulfate (GSTS) was included in the standard series in Malmö in 1991, a surprisingly high frequency, about 10%, of positive patch tests was found (1, 2). Since then it has been shown that the positive patch test is a manifestation of contact allergy (3–9). Other authors have also found high frequencies of gold allergy (10–15). The relevance of this contact allergy and how the patients are sensitized are important questions to be answered. A questionnaire study in consecutively patch-tested dermatitis patients in Malmö (2) and recently from the USA (16) indicated a relationship between gold allergy and the presence of dental gold restorations. Such a relationship has also been confirmed in a prospective, controlled dermato-odontological study (17). For a metal to sensitize, ionization is considered necessary. Dental gold alloys are resistant to corrosion, and it may be questioned whether they can corrode to such an extent that sensitization is possible. A higher blood concentration of gold in patients with dental gold compared to those without would indirectly indicate an ionization of dental gold. A recent study clearly indicates that gold is released from dental restorations and that there are associations between gold concentrations in different biological media on the one hand, and the number of dental gold restorations on the other (18). However, a large majority (86%) of the results for the concentration of gold in whole blood (B-Au) were below the detection limit. The aim of the present work was to determine B-Au using the highly sensitive inductively coupled plasma mass spectrometry technique and to study relationships between B-Au and the number of dental gold restorations in persons with and without contact allergy to gold.

Materials and methods

Patient material

Patients under investigation, including patch-testing, for suspected contact dermatitis at the Departments of Dermatology and Occupational and Environmental Dermatology in Malmö were invited to participate in a parallel odontological study. Patients referred for oral complaints or lesions were not accepted in the study; for practical reasons, only patients living in Malmö and immediate surroundings were included. The patients in the present study belonged to a larger group of 102 patients in which the relationship between contact allergy to gold and dental gold restorations was studied (17). Of these, 80 patients (36 M, 44 F) volunteered to have a blood sample for gold determination before the epicutaneous testing.

* Dr Schütz died on 30 July 2001.

Epicutaneous tests

The patients were patch-tested on the back with the dental screening series, including various titanium compounds, the European standard series (Chemotechnique Diagnostics, Tygelsjö, Sweden) and, when indicated, with additional test series as well as patient-supplied materials. Test substances, which were included in the standard series, were excluded in the dental test series. In addition, 2.0% and 5.0% GSTS (wt/wt in petrolatum) were included. Finn chambers® (Epitest, Tuusula, Finland) were attached with Scanpor tape® (Norgesplaster, Vennesla, Norway). The patches were removed after 2 days by the patient and the reactions read after a further day (Day 3) and on Day 7 according to the criteria of the International Contact Dermatitis Research Group (19).

Blood sampling and storage

Before patch-testing, venous blood was drawn from a cubital vein into heparinized 10 mL tubes (Venoject, VP-100 SHL, Terumo Europe N.V., Leuven, Belgium). The blood samples were transferred to acid-washed polypropylene tubes (Sarstedt, Nünbrescht, Germany) and stored deep-frozen (−20°C). At analysis, the content of the tubes was homogenized using an ultrasonic probe (VibraCell VC-100, Sonic and Materials Inc., Danbury, Connecticut, USA).

Gold determination

Gold (Au) was determined by inductive couple plasma mass spectrometry (ICP-MS; PQ2+ from Fisons Elemental, Winsford Cheshire, UK) equipped with a Gilson 222 auto sampler (Gilson, Villiers, France). The samples were diluted 10 times with a solution containing 5 g/L of 25% ammonia (ARISTAR, Merck, Poole, UK) 0.5 g/L Triton X-100 (Sigma, St Louis, Mo., USA) and 0.5 g/L ethylenediaminetetraacetic acid disodium salt dihydrate (pro analysi, Janssen Chimica, Geel, Belgium) in ultra pure water from a USF Elga Maxima (Buckinghamshire, UK) water purification system according to Barany et al. (20). The samples were prepared in acid-washed screw-capped polypropylene test tubes. Internal standards, indium and thallium (AccuStandard Inc, New Haven, Ct., USA) were added to a concentration of 20 μg/L in the final sample dilution. All samples were prepared in duplicate. Blood samples spiked with 5 μg/L Au were used for method calibration. Using diluent as a carrier/rinsing fluid, the samples were introduced in a segment flow mode. A water chilled spray chamber (Scott, 7C), a PTFE V-groove nebulizer and nickel sampler and skimmer cones were used (Thermo Elemental, Winsford, Cheshire, UK). The gas flows were 13.0 L/min for the cooling gas, 1.1 L/min for the auxiliary gas and 0.96 L/min for the nebulizer gas. The forward power was 1350 W, and reflected power <5W. The sample flow was 1.0 ml/min. The acquisition time was 12 s and the samples were analyzed in peak-jumping mode for ^{115}In, ^{197}Au and ^{205}Tl (3 points per peak, 15.24 ms dwell time for internal standards and 75.24 ms for Au).

The detection limit (defined as $3 \times s$ for reagent blanks) was 0.04 μg/L. The method reproducibility, calculated as the coefficient of variation (CV) for the duplicate determinations with values above the detection limit, was 7% ($n = 37$; mean 0.13 μg/L). When including the results of samples with values below the detection limit, CV increased to 11%.

Since no certified reference samples for B-Au are available, outdated blood from blood donors spiked with 0.1 and 1.0 μg/L Au was used for assessment of the analysis method. Our B-Au results averaged 0.10 (range 0.08–0.13; $n = 3$) μg/L and 1.01 (range 0.96–1.07; $n = 3$) μg/L, respectively.

Odontological examination

The clinical oral examination consisted of registration of the number of teeth and number of surfaces with reconstructions. The following materials were registered: Amalgam, composite or acrylic reconstructions as in the case of partial dentures, glass ionomer cement, gold alloys, ceramics, titanium and non-noble alloys. The number of restored surfaces of a tooth was quantified as follows: 0 = No surface covered; 1 = one surface covered; 2 = two surfaces covered; 3 = three or more surfaces covered; 4 = an artificial crown covering the tooth.

In addition, a gold post was registered as one surface. The clinical data were further analyzed and compared to panoramic radiographs since, for example, in the case of gold posts, these can be detected in radiographs only.

All the odontological examinations, patch tests and blood analyses were performed without knowledge of the results from the other investigations. The study was approved by the Ethics Committee of the Faculty of Medicine, Lund University.

Statistical analyses

Calculations were carried out with the Mann-Whitney U-test and Spearman rank correlation. All data from blood analyses were used for calculations. Thus, results below the detection limit were not rejected or changed so that distribution or median values would not be distorted.

Results

Of the 80 patients, 43 (25 F, 18 M) had dental gold restorations. The median number of dental gold surfaces in this group was 17 (range 4–84). In the entire material, the median B-Au was <0.04 (range <0.04–1.07) μg/L. One woman patient with an extremely high B-Au (1.07 μg/L) had 73 surfaces with dental gold. When this patient was excluded, the remaining B-Au values ranged between <0.04 and 0.20 μg/L. However, only about 50% of the

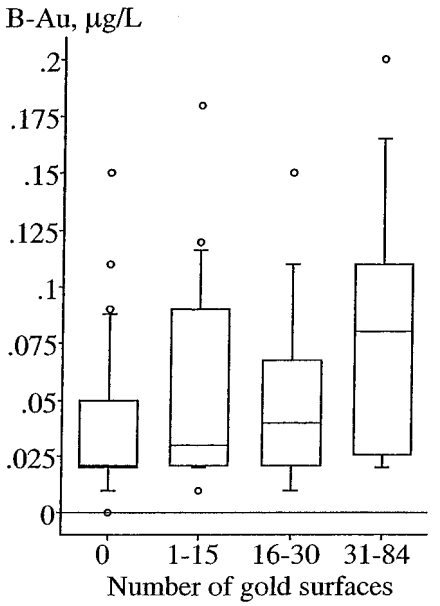

Fig. 1. Relationship between the concentration of gold in whole blood (B-Au) and the number of gold surfaces in dental restorations in 79 dermatitis patients is shown. The patient with B-Au 1.07 µg/L and 73 surfaces excluded. The box is defined by the upper and lower quartiles and with the median marked by a subdivision of the box. The whiskers are the lines that extend from the top and bottom of the boxes to the lowest and highest observations, excluding outliers (circles).

values were above the theoretical detection limit (0.04 µg/L) calculated as $3 \times s$ for the reagent blanks. The B-Au was higher in patients with dental gold restorations (median 0.04 µg/L; range <0.04–1.07 µg/L) than in those without (median <0.04 µg/L; range <0.04–0.15 µg/L) ($P = 0.025$, Mann-Whitney U-test) (Fig. 1). There was a positive correlation between B-Au and the number of dental gold restorations (Spearman's rank correlation; $r_s = 0.32$, $P < 0.01$). When the patient with the highest B-Au was excluded, there was still a significant correlation ($r_s = 0.30$, $P < 0.01$). When the patients were grouped according to gender, the correlation was significant for women ($n = 44$, $P = 0.018$) but not for men ($n = 36$; $P = 0.229$). If the female with the highest B-Au was excluded, there was still a significant correlation for women ($P = 0.04$). In those with gold restorations the number of gold surfaces was numerically but not statistically significantly higher in females than in men (median 21 and 16, respectively).

When comparing men and women without dental gold, there was no statistically significant difference in B-Au ($P = 0.90$).

The median age was higher in the group with dental gold (51 years) than in the group without (33 years) and there was a strong correlation between the amount of dental gold and age ($P = 0.0001$). Looking exclusively at the patients without dental gold, there was a tendency, though not statistically significant ($P = 0.075$), for decreasing B-Au with increasing age. The presence of gold posts was strongly correlated to the number of dental gold surfaces, so it was not possible to look exclusively at B-Au in relation to gold posts. There was no correlation between B-Au and the number of amalgam surfaces.

Twenty-three patients (29%) were gold-allergic and had a significantly higher number of gold surfaces ($P = 0.0189$) (median 16, range 0–71) than patients not allergic to gold (median 0; range 0–84). The gold-allergic patients had a numerically higher B-Au (median 0.04 µg/L; range <0.04–0.15) compared to patients without gold allergy (median <0.04 µg/L; range <0.04–1.07). The difference, however, was not statistically significant ($P = 0.07$).

Discussion

Only a few studies containing data on B-Au in the general population were found in the literature (18, 21, 22). Minoia et al. (21) reported a mean of 0.045 ± 0.0007 µg/L ($\pm s$; $n = 35$; range 0.002–0.06 µg/L) obtained by use of neutron activation analysis. Our results are in reasonable agreement with these data. No information about dental gold restorations was given by Minoia et al. (21). A higher B-Au, a mean of 0.22 µg/L, range 0.131–0.41 µg/L, obtained by sector field inductively coupled plasma mass spectrometry, was reported by Begerow et al. (23) in 7 individuals with no known exposure to precious metals.

Drasch et al. (18) determined gold in whole blood and other biological media using graphite furnace atomic absorption spectrometry with Zeeman background correction. In that study, all subjects without gold restorations ($n = 16$) had B-Au below the detection limit, 2 µg/L, while 16 of 65 subjects with 1–14 noble metal restorations had

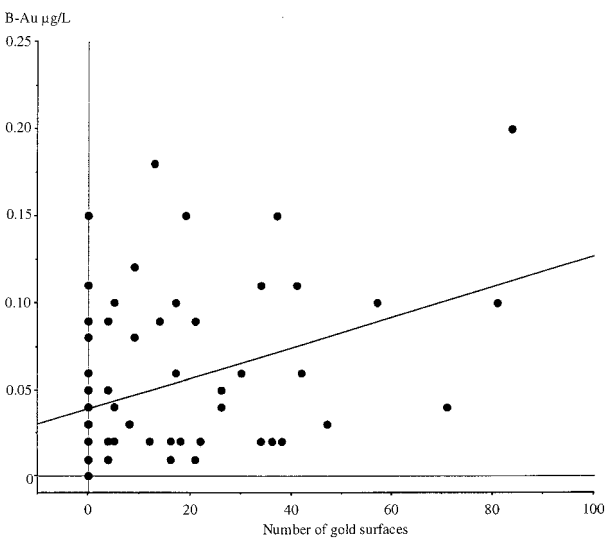

Fig. 2. The correlation between blood levels (B-Au) and number of gold surfaces in 79 dermatitis patients. The patient with the highest B-Au level excluded. The regression line is shown ($Y = 0.00089X + 0.39$; $r_s = 0.30$).

detectable B-Au (range 2–9.1 μg/L). Significant correlations were obtained between the concentrations of gold in whole blood, serum, saliva, urine and faeces, on the one hand, and the number of noble metal restorations, on the other. Thus, the data of Drasch et al. might indicate a B-Au distribution towards considerably higher levels than seen in our study. However, analytical problems caused by contamination or unspecific background absorption, resulting in falsely high results in that study, may be suspected. For example, the maximum gold concentration in serum of 29.9 μg/L reported for a subgroup of subjects is incompatible with a maximum B-Au of 4.2 μg/L in the same group.

In spite of the relatively low B-Au values in the present study, we found significantly higher B-Au in patients with dental gold restorations than in those without. The patients with dental gold restorations were older than the patients without dental gold, and there was a strong correlation between the amount of dental gold and age. However, looking exclusively at the patients without dental gold, there was a tendency towards decreasing B-Au with increasing age, which together with the dose-response relationship between B-Au and the number of dental gold surfaces strongly indicates that dental gold is an important predictor of B-Au in persons with dental gold restorations. It would be interesting to exclusively study the relationship between gold posts and B-Au, since theoretically there is a possibility for direct uptake of gold ions via the root canal and through the root and dentine tubules into the blood vessels. It was not possible to do this, however, since all the patients with posts also had other dental gold restorations and the posts correlated strongly to gold surfaces.

Our results verify that gold is released from dental gold restorations and taken up into the circulation. Possible routes of gold absorption are via the oral mucosa or the gastrointestinal tract, and directly by uptake in blood from gold posts. For this to occur, an ionization of the metallic gold is considered to be required. Gold has been reported not to be soluble in artificial sweat (24). However, Flint points out that the corrosive media that dental alloys are exposed to might be distinctly different from that of sweat (25). Brown et al. showed that metallic gold is soluble in a range of aqueous amino acids (26). Drasch et al. (18) analyzed the concentration of gold in saliva and found higher values in persons with dental high gold alloys compared to those without. Furthermore, it has been demonstrated by Begerow et al. (23) that a corrosion and dissolution of Au occurs from dental gold alloys in artificial saliva as well as lactic acid solutions. It is known that temperature and factors that can be influenced by the oral hygiene and periodontal status such as number of micro-organisms, pH and oxygen concentration can have an effect on the process of corrosion. The type of gold alloys used can also be significant for the rate of dissolution. For example, the higher the copper content in the gold alloy the more gold is dissolved, perhaps due to the increased surface area exposed by the dissolving copper (26).

We detected gold in blood also in patients without dental gold. Almost everyone has or has had gold jewelry in close skin contact. However, it is unlikely that the amount of gold ions released from jewelry could be the main supply of the gold found in blood. Another explanation could be sample contamination at sampling or analysis even though measures were taken to reduce that risk. Nevertheless, since the present study is double-blind, a possible contamination could not explain the difference in B-Au between patients with and without dental gold restorations. To our knowledge, other sources of gold uptake in the general population, such as drinking water and foodstuffs, have not been investigated. An odd source of intake of metallic gold is some special liquors decorated with free-floating gold flakes (27). Russell et al. reported 3 cases of lichenoid dermatitis after consumption of cinnamon schnapps with gold flakes (27). Gold is, to some extent, dissolved in the liquor. Elevated levels of gold in urine and blood (0.4 mg/L) were present in a patient 3 months after consumption of this beverage (27).

Not unexpectedly, gold-allergic patients had numerically higher B-Au, since we have previously shown that gold-allergic patients have a higher amount of dental gold surfaces (17). Patients with eczematous disease show an overrepresentation of gold allergy among those with dental gold (2, 16). We found a similar significant association in a recent, double-blind parallel dermato-odontological study (17). Furthermore, among patients examined for oral complaints, an association between gold allergy and gold restorations has been demonstrated (28).

A fundamental question is, of course, whether the raised B-Au caused by dental gold has any clinical relevance. In a study in which gold allergic patients were provoked with 10 mg intramuscularly administered gold sodium thiomalate, a majority of the patients (80%) had a flare up of previous positive GSTS patch tests (29). Interestingly, many of the patients also had systemic symptoms; 46% had a rash and 60% had a transient fever accompanied by an influenza-like feeling. The B-Au levels in that study were obviously very much higher than the values in the present one. Nevertheless, the question whether low-grade chronic symptoms may appear correlating to the raised B-Au in patients with dental gold *and* gold allergy remains unanswered.

Acknowledgements.—This study was supported by grants from the Swedish Foundation for Health Care Sciences and Allergy Research and the Swedish Asthma and Allergy Association.

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Received for publication 17 December 2001
Accepted 26 April 2002