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Levels of gold in plasma after dental gold inlay insertion

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Abstract

Objective. Several studies have reported increased levels of gold (Au) in the blood of patients with dental gold restorations. This study analyzed gold levels in blood plasma before dental gold inlay insertion, 0–12 months after, and 15 years after. ***Material and Methods.*** Plasma samples from 9 patients were taken before and 0–12 months after gold inlay insertion. Fifteen years after gold inlay insertion, further blood samples taken from 8 of these patients were analyzed for gold using inductively coupled plasma mass spectrometry. An oral examination was also carried out before and 15 years after gold inlay insertion. ***Results.*** Gold levels in plasma were significantly higher 0–12 months after gold inlay insertion than before treatment ($p = 0.008$). No significant difference in gold plasma levels was found between 0–12 months after and 15 years after insertion ($p = 0.109$), although there was a significant correlation between the number of gold alloy surfaces and the amount of gold in plasma 15 years after insertion ($p = 0.028$). ***Conclusions.*** This study supports a dose-related release of gold into plasma from dental gold restorations, a release that appears to be stable over time.

Key Words: *Analysis, delayed hypersensitivity, gold (Au), plasma*

Introduction

Of various materials used in rehabilitation of the oral cavity, gold (Au) alloys have long been the material of choice for more extensive restorations because of their resistance to corrosion. Some *in vitro* studies, however, have shown dissolution of metallic gold due to interaction with bacteria [1], amino acids, or pH [2].

Several studies have also shown a relationship between dental gold alloys and contact allergy to gold [3–5]. One Swedish study found that 10% of consecutively patch-tested dermatitis patients had a contact allergy to gold [6]. Gold was the second most common allergen after nickel, but its clinical relevance may be lower, although this is not clear. Comparable results have been found in a retrospective multicenter study of patch-test reactions with a dental screening series in Finland [7], in which contact allergy to gold was on average 7.7%, varying between 4.1% in one clinic and 15.0% in the clinic with the highest prevalence. The study reported that gold was the third most common allergen after nickel and mercury.

Gold release from dental gold alloys and subsequent elevation of gold levels in blood have been observed previously [8]. The significance of elevated levels of gold in plasma remains unclear. Injection of 10 mg gold sodium thiomalate (Myocrisin®) intramuscularly in gold-allergic patients produces clinical toxicoderma-like rash reactions, transient fever and eczematous flare-up of sites of previous dermatitis and previously positive patch tests [9]. Several studies also report metal allergy as a risk factor for oral lichen planus (OLP) and oral lichenoid lesions (OLL) [10–13].

This study aimed to measure gold in blood plasma before, 0–12 months after, and 15 years after insertion of dental gold inlays in patients, to test the hypothesis that gold is constantly released from dental gold alloys, and to correlate the number of dental gold surfaces with gold levels in plasma.

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Material and methods

Patients

Ten healthy patients (the experimental group) and their spouses (the controls) had participated in a previous Swedish study measuring the concentrations of several metals in blood and urine before and after amalgam removal and subsequent gold inlay insertion [14]. One patient died within the first year of the study and the plasma samples taken from this patient were therefore not included in the study.

Plasma samples taken before and 0–12 months after gold inlay insertion from the 9 patients were stored as indicated below. Further plasma samples were taken 15 years after insertion from 8 of the 9 patients (one patient had moved away and could not attend the follow-up study). The mean age of the 8 patients (4 M and 4 F) was 50 years (range 44–60 years).

Gold inlay insertion, blood sampling and storage

Blood samples from each of the patients were drawn from the cubital vein before and 0–12 months after removal of the amalgam fillings, and collected in metal-free tubes (Venoject®, VP-100 SHL; Terumo Europe N.V., Leuven, Belgium) with heparin as an anticoagulant. The samples were centrifuged at 2000*g* for 10 min, and while the supernatant plasma was initially stored at -80°C it was later moved to -20°C owing to changed laboratory procedures.

All amalgam fillings were removed and preparation and impression for the gold inlays were carried out according to standard clinical procedures at the same time-point. Temporary restorations (Nobetec®; Ängelholm, Sweden; or zinc oxide-eugenol cement) were placed, and about 15 days later gold inlays were permanently cemented with zinc phosphate luting cement (Phosphocap®; Ivoclar, Schaan, Liechtenstein). A total of 113 teeth were restored with gold inlays (JS C3 gold; AB John Sjödings, Kista, Sweden), i.e. a mean number of gold inlays of 11 per patient distributed over an average of 19 surfaces in each subject.

The blood samples taken 15 years after insertion were also drawn from the cubital vein into heparinized 10 ml tubes (Venoject®, VP-100 SHL; Terumo Europe N.V., Leuven, Belgium) and centrifuged at 2000*g* for 10 min. The supernatant plasma was then stored at -80°C.

Gold determination

The concentration of gold in plasma was determined by inductively coupled plasma mass spectrometry (Thermo X7; Thermo Elemental, Winsford, UK) equipped with a conical glass nebulizer (Glass Expansion, Melbourne, Australia) with 1 ml/min uptake and a peltier-chilled, conical impact bead spray chamber (Thermo Elemental, Winsford, UK). The gas flows were 13 l/min for the cooling gas, 1.1 l/min for the auxiliary gas, and 0.93 ml/min for nebulizer gas. The plasma samples were diluted 5 times with an alkaline solution following Bárány et al. [15]. Using the diluent as a carrier/rinsing fluid, the samples were introduced in a segment-flow mode. They were analyzed in peak-jumping mode, 100 sweeps and 1 point per peak, and 50 ms dwell-time for ^{181}Au and 10 ms dwell-time for bismuth (^{181}Bi) were used as internal standard. The detection limit, calculated as 3 times the standard deviation (SD) of the blank, was 0.005 μg/l. Method imprecision calculated as the coefficient of variation for duplicate measurements was 8% in the concentration range <0.01–0.43 μg/l. Because no certified reference sample for plasma gold is available, outdated plasma from blood donors spiked with 0.10 μg gold/l was used for assessing the analysis method. A measurement of 0.093 ± 0.008 (mean $\pm$ SD; $n = 5$) was obtained.

Clinical examination

Number of teeth and presence of restorations were recorded, and a short questionnaire mainly concerning medication was answered by the patients.

Informed consent and ethical approval

Informed consent was obtained from participants in the study, and the study itself was approved by the Ethics Committee of the Faculty of Medicine, Lund University, Lund, Sweden.

Statistical analyses

Statistical analyses were conducted using SPSS release 13.0 (SPSS Inc., Chicago, Ill., USA). *P*-values <0.05 were regarded as significant. Wilcoxon's signed-rank test, Spearman's rank correlation and two-tailed tests were applied.

Results

The gold concentration of plasma was significantly higher in samples collected 0–12 months after gold inlay insertion (median 0.27; range 0.15–0.79 μg/l) ($p = 0.008$, Wilcoxon's signed-rank test; with Bonferroni correction: $p = 0.024$) and also 15 years after (median 0.16; range 0.04–0.42 μg/l) ($p = 0.012$, Wilcoxon's signed-rank test; with Bonferroni correction: $p = 0.036$) compared with samples collected before gold inlay insertion (median 0.03, range 0.02–0.05 μg/l) (Table I). However, there was no statistically significant difference in gold concentration between the samples collected 0–12 months after and 15 years after insertion ($p = 0.109$, Wilcoxon's signed-rank test). A statistically significant

Table I. Gold in plasma (μg/l) before dental gold inlay insertion, 0–12 months after, and 15 years after, and total number of surfaces of gold directly after gold inlay insertion and 15 years after.

Patient no.	Total number of gold surfaces directly after gold inlay insertion	Total number of gold surfaces 15 years after gold inlay insertion	Au in plasma (μg/l) before gold inlay insertion	Au in plasma (μg/l) 0–12 months after gold inlay insertion	Au in plasma (μg/l)15 years after gold inlay insertion
1	18	18	0.05	0.15	0.12
2	*	*	0.03	0.17	*
3	15	15	0.05	0.15	0.14
4	21	20	0.02	0.38	0.22
5	38	36	0.03	0.34	0.42
6	38	29	0.03	0.23	0.19
7	19	19	0.02	**	0.13
8	13	2	0.02	0.30	0.04
9	9	9	0.02	0.79	0.18

* No clinical examination performed (patient is no longer living in Sweden).
** No sample available for analysis.

correlation was found between the number of gold surfaces and gold levels in plasma collected 15 years after gold inlay insertion ($p = 0.028$, Spearman's rank correlation; two-tailed test). No such correlation was found 0–12 months after gold inlay insertion ($p = 0.726$, Spearman's rank correlation; two-tailed test). In two patients (numbers 6 and 8), 9 and 11 gold inlays, respectively, were successively removed due to hypersensitivity and/or caries/loss of retention.

No patient reported being on medication with gold-containing drugs.

Discussion

The gold concentrations in plasma in the present study were comparable to those reported previously by Ahnlide et al. [8], in whose study patients with dental gold restorations had a statistically significantly higher level of gold in the blood (range <0.04–1.07 μg/l) than patients without (range <0.04–0.15 μg/l). The number of surfaces with dental gold also correlated with the gold levels in plasma, both in this and in the previous study [8]. Gold levels 0–12 months after dental gold inlay insertion, however, did not correlate with the number of surfaces with dental gold. It should be noted that no information was available on the exposure time to dental gold in the previous study [8].

The effect of elevated gold levels in blood remains unclear, but there is a strong correlation between dental gold and both an increased risk of contact allergy to gold [3–7] and increased gold blood levels [8].

Garhammer et al. [16] suggest that the metal content of saliva is affected by intraoral restorations, but that this is not a reliable indicator of the systemic exposure to metals released from the oral cavity. This may be supported by the wide variation in gold and chromium levels found in the two samples from each patient in that study. Another study analyzed metals in biopsies from patients with intraoral complaints [17]. Silver, gold, copper, and lead levels were significantly higher at the affected sites (gingiva and mucosa with adjacent restorations) compared with healthy control sites. Drasch et al. [18] found that gold concentrations in all biomonitors (saliva, urine, feces, whole blood, and plasma) reflected the number of teeth with noble metal restorations.

Chewing gum and coffee consumption are associated with higher levels of gold in blood in subjects with dental gold [19]. The general population's environmental exposure to gold is not well documented, but in a clinical setting gold salts are used in rheumatoid arthritis therapy and gold is used in intracoronary stents [20] and renal-artery stents [21]. There have been reports recently of an increased risk of contact allergy to gold in patients with gold-plated intracoronary stents [20] and also an increased risk of restenosis with gold-coated renal artery stents [21]. Svedman et al. [20] found statistically significant differences in the frequency of contact allergy to gold in patients with gold-plated intracoronary stents compared with a control group. Contact allergy to gold was found in 45.5% of the stent group ($n = 22$), but only in 20.5% of the control group ($n = 88$). This indicates that gold also dissolves from stents, and may lead to sensitization and an increased risk of development of contact allergy to gold.

Metal release from removable partial dentures with a cast framework has also been described, notably the release of cobalt and chromium into saliva, with newer and larger dentures releasing greater quantities [22]. The authors suggest that this indicates an inverse relationship between metal release and age of the denture, whereby the alloys passivate over time due to deposits that reduce the corrosion. In contrast, the present study finds that gold levels in plasma do not differ 0–12 months after and 15 years after gold inlay insertion, which may indicate a constant release of gold.

The effects of removing dental gold alloys on gold levels in blood have not been reported. Mercury

levels in blood before and after amalgam removal in humans, however, correlate with the total number of amalgam surfaces and the total surface area of the fillings [14]. Plasma mercury levels rose initially after amalgam removal, declining within a month to pre-removal levels. Twelve months after removal, the levels were 25–50% of the pre-removal values.

Although a small sample population was used in the present study, the results are of value because the patients were observed closely for more than 15 years and long-term studies of plasma gold levels are few.

Storing plasma samples at -20°C over extended periods is risking dehydration. Because no statistical difference was found in plasma gold levels 0–12 months after and 15 years after dental gold inlay insertion, it may be assumed that these samples are not dehydrated.

Previous results have indicated that gold levels in blood, from patients who lack dental gold, decrease with increasing patient age [8]. The present study indicates a relatively stable elevated level of gold in plasma over time after dental gold inlay insertion, thus supporting the hypothesis that gold is constantly released from dental gold alloys in the oral cavity.

Further studies are needed to clarify how gold is dissolved and to evaluate the possible role of gold and contact allergy to gold in oral disorders such as oral lichen planus and lichenoid reactions.

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