

Suzuki Kayoko (Orcid ID: 0000-0001-8367-1034)
Nishioka Kazue (Orcid ID: 0000-0002-5361-7843)

Multicenter one-month follow-up study of the patch test reaction to the gold sodium thiosulfate of the TRUE test and its association with piercings and dental metal history

Kayoko Suzuki^{*1)20)}, Kayoko Matsunaga¹⁾²⁾²⁰⁾, Akiko Ito²⁾³⁾²⁰⁾, Akiko Yagami¹⁾²⁰⁾, Takashi Ito⁴⁾²⁰⁾, Hitoshi Miyazawa⁵⁾²⁰⁾, Mariko Sugiura⁶⁾²⁰⁾, Atsuko Adachi⁷⁾²⁰⁾, Yumiko Kubota⁸⁾²⁰⁾, Yuko Watanabe⁹⁾²⁰⁾, Atsuko Kato¹⁰⁾²⁰⁾, Kazue Nishioka¹¹⁾²⁰⁾, Atsushi Fukunaga¹²⁾²⁰⁾, Masako Mochizuki¹³⁾²⁰⁾, Yuko Ikezawa¹⁴⁾²⁰⁾, Takahiko Tsunoda¹⁵⁾²⁰⁾, Kaoru Takayama¹⁶⁾²⁰⁾, Kumiko Washizaki¹⁷⁾²⁰⁾, Hiroo Yokozeki¹⁶⁾²⁰⁾, Takuma Ishihara¹⁸⁾, Hideo Asada¹⁹⁾²⁰⁾, Hiromi Kanto⁴⁾²⁰⁾

- 1) Department of Allergology, Fujita Health University School of Medicine
- 2) Department of Integrative Medical Science for Allergic Disease, Fujita Health University School of Medicine
- 3) Department of Dermatology, Nagata Clinic
- 4) Department of Dermatology, Toho University Omori Medical Center
- 5) Nishi-Sapporo Skin and Allergy Clinic
- 6) Environmental Dermatology & Allergology, Daiichi Clinic
- 7) Department of Dermatology, Hyogo Prefectural Kakogawa Medical Center
- 8) Department of Dermatology, Fukuoka Sanno Hospital
- 9) Watanabe Skin and Plastic Surgery Clinic
- 10) Department of Dermatology, Gokeikai Osaka Kaisei Hospital
- 11) Joy Dermatological Clinic
- 12) Division of Dermatology, Department of Internal Related, Kobe University Graduate School of Medicine
- 13) Mochizuki Dermatological Clinic
- 14) Department of Dermatology, Chigasaki Municipal Hospital
- 15) Department of Dermatology, Yamagata City Hospital SAISEIKAN
- 16) Department of Dermatology, Tokyo Medical and Dental University Medical Hospital
- 17) Omorimachi Dermatology
- 18) Innovative and Clinical Research Promotion Center, Gifu University Hospital
- 19) Department of Dermatology, Nara Medical University Hospital
- 20) Japanese Contact Dermatitis Research Group

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the [Version of Record](#). Please cite this article as doi: [10.1111/cod.13827](https://doi.org/10.1111/cod.13827)

This article is protected by copyright. All rights reserved.

Corresponding author: Kayoko Suzuki

Department of Allergology, Fujita Health University Second Educational Hospital

3-6-10 Otobashi, Nakagawa-ku, Nagoya, Aich 454-8509, Japan

Phone: +81-52-321-8171; Fax: +81-52-322-4734

E-mail: kayokos@fujita-hu.ac.jp

Conflicts of Interest: KM is employed in an endowed department that is sponsored by Hoya Co., Ltd. The rest of the authors have no conflict of interest to declare.

Abstract

Background: There is controversy over late and long-lasting reactions to gold sodium thiosulfate (GST).

Objectives: To study the GST patch test reaction by observing the application site after 1 month, and to clarify the relevance of GST sensitization by piercings and dental metals.

Patients: A retrospective analysis was performed on 746 patients (143 males; 603 females) who were patch tested using GST of the TRUE test. We conducted a questionnaire on the presence of piercings or dental metals in these patients.

Results: The GST positive rate was 27.9% at Day 3 and/or Day 7 and 40.3% up to the 1-month reading. The positive rate was significantly higher in females and increased with age. Sixty-two percent of cases with a positive reaction at Day 7 continued to show a positive reaction after 1 month. Eleven percent of cases with a negative reaction at Day 3 and Day 7 showed a late reaction. Both piercings and dental metals were related to gold sensitization.

Conclusions: The GST of the TRUE test had a high positive and low false negative rate. The 1-month reading after the patch test was important for identifying late reactions. Piercing history and dental metal were associated with gold sensitization.

Key words:

Gold sodium thiosulfate, Patch testing, Late reaction, Long lasting reaction, Piercing, Dental metals

Introduction

The patch test has been used to detect gold allergy using gold sodium thiosulfate (GST), gold sodium thiomalate, and chloroauric acid.^{1,2} Recently, GST has been used as a gold patch test reagent. Initially, GST was patch tested at 0.5% in petrolatum (pet). However, Malinauskiene et al. report that there are many false-negatives using GST 0.5% pet, and GST 2% pet is the optimal concentration.³ Panel 3 of the TRUE test, which is a patch test reagent for ready-to-use products released in 2012, has a GST at concentration of 0.075 mg/cm², so as to have a positive rate similar to GST 2% pet.⁴ In Japan, the TRUE test, which has been reconfigured as a Japanese baseline series, was released as Patch Test Panel™ (S) (Sato Pharmaceutical Co., Ltd, Tokyo, Japan) on May 2015.

We have reported that the GST of the TRUE test has a positive rate higher than GST 0.5% pet, that there have been cases in which the positive reaction occurred after the day 7 (D7) reading, and the positive reaction persists for a long time.⁵ It is well known that gold causes a late reaction in the patch test, which is considered to be a reaction in a sensitized case, not an active sensitization.^{6,7} However, the previous reports are case reports of a late reaction^{8,9,10} and clinical studies targeting sensitized cases.^{6,7} There are few reports confirming the frequency of a late reaction and a long-lasting reaction to GST in all patch cases. In this study, we observed GST patch test cases up to 1 month later, investigated the positive rate, the duration of a positive reaction, the frequency of a late reaction, and examined the association with piercings and dental metal in positive cases.

Patients and Methods

Patients: Patients were patch tested using the GST of the TRUE test from January 2017 to September 2018 and had the GST application site observed up to 1 month at participating departments. All patients answered the questionnaire about the presence of piercings and the presence of dental metals. Most patients answered the questions before the patch test, but some responded after the patch test. Most metals used for dental treatment in Japan contain gold; therefore, the patients were only asked whether they currently had dental metal in their mouth.

Methods: The TRUE test containing 0.075 mg/cm² GST in a hydroxypropyl cellulose gel vehicle was applied to the upper back of patients for 2 days (application day was Day 0). After removing the test unit, we evaluated the reactions according to International Contact Dermatitis Research Group criteria on Day 2, Day 3 (D3), Day 7 (D7) and 1 month after the patch test. A positive reaction was diagnosed if a + or

stronger reaction was observed on D3, D7 or at 1 month. A questionnaire survey was conducted on all cases regarding their piercing history and the presence of dental metals.

We analyzed the positive ratio of GST, age distribution of GST positive cases, long-lasting reaction ratio of a positive reaction to GST, ratio of a late reaction to GST. We performed a statistical analysis on the relationship between gold positivity and a piercing history and/or the presence of dental metals.

This study was approved by the ethics committee of The University of Toho, which was the main research facility (approval no. M17114), and the institutional review board of each participating site. The study was carried out in accordance with the Declaration of Helsinki and informed consent was obtained from subjects prior to their inclusion in the study.

Statistical Analysis: Patients' characteristics were summarized using the mean and SD for continuous variables, and frequencies and percentages for categorical variables. The patients were divided into four groups. Group A had no dental metals and no piercings. Group B had no dental metals but had piercings. Group C had dental metals, but did not have piercings, and Group D had both dental metals and piercings. We compared the proportion of gold positivity between the 4 groups using a multivariable logistic regression model adjusted for age and sex. The odds ratios (OR) of Groups B, C, and D to Group A were used to evaluate the association between gold positivity and a piercing history and/or the presence of dental metals. The logistic regression models were constructed with positive up to D7 and positive up to 1 month as outcomes, and the association was assessed in each model. In addition, to compare the difference of proportion in gold positivity at D3 and/or D7 and up to 1 month, a generalized estimating equation (GEE) model with the logit link function was constructed. The GEE model included age and sex as covariates, and the interaction term between time points and groups. We recognized the difference in proportion when the interaction terms of Groups B, C, or D to Group A were significant. All analyses used a two-sided 5% significance level and were performed using R version 3.6.2 (<http://www.r-project.org>).

Results

Patients

A total of 746 patients (143 males with a mean age of 48.9 ± 18.0 years, and 603 females with a mean age of 49.1 ± 17.2 years) were enrolled in this study (Table 1).

Positive ratio to GST

A total of 208 (27.9%) of 746 cases showed a positive reaction on the D3 and/or D7 reading (Table 2). In 538 cases that showed a ?+, irritant reaction (IR), negative reaction to GST on the D3 and D7 readings, 93 cases had a positive reaction at the 1-month reading. Since there were 301 cases with a positive reaction to GST up to 1 month after the patch test, the positive rate up to the 1-month reading was 40.3%. Of the 301 cases that had a positive GST reaction up to 1 month, 21 (7%) cases had no piercing history nor dental metal, and the other gold sensitization source was unknown (Table 2).

Ratio of a long-lasting reaction to GST

Of the 208 cases with a positive reaction on the D3 and/or D7 reading, 129 cases (62.0%) continued to have a positive reaction at the 1-month reading (Table 2). It was thought that more than half of cases with a positive reaction to GST on D3 and/or D7 reading continued after 1 month. There was no clear association between the intensity of the patch test reaction on D3 or D7 reading and the presence of a positive reaction after one month. (Table 3a).

Ratio of a late reaction to GST

A total of 93 (17.3%) of the 538 cases that were not positive on the D3 and D7 readings showed a positive reaction at 1 month after the patch test (Table 3a). Approximately 30% of the cases whose strongest reactions are ?+ or IR on D3 or D7 reading, showed a positive reaction at the 1-month reading. For 378 patients who were negative for both D3 and D7 readings in Table 3a, the 1-month reading was compared according to the presence or absence of piercings and dental metal in Table 3b. In Table 3b, of the 378 cases that were negative at D3 and D7 readings, 337 cases had dental metals or piercings, and 33 cases (9.8%, 33/337) were positive at the 1-month reading. On the other hand, of the 378 cases, 41 cases had neither dental metals nor piercings, and 7 cases (17.8%, 7/41) were positive after the 1-month reading.

Results from the statistical models (Tables 4 and 5)

a) The relationship between gold positivity and a piercing history and/or the presence of dental metals (Table 4 and Fig. 1)

In the positive cases on the D3 and/or D7 reading, only Group D was significantly different from Group A (OR, 3.6; 95% confidence interval (CI), 1.6 – 8.09; $P =$

0.002). It was suspected that both dental metal and piercings were related to gold sensitization. In the cases that were positive up to the 1-month reading, there was no significant difference between any group.

b) The increases in the proportion of positive reactions between the D3 and/or D7 reading and the 1-month reading in each group (Table 5)

The increases in the proportion of positive reactions were: 20.6% in Group A, 22.8% in Group B, 11.1% in Group C, and 10.5% in Group D. In addition, “Group * period” which indicates the interaction between groups (A, B, C, and D) and the periods (D3/D7 reading and 1 month reading) were also confirmed. The interaction of Group C * period and interaction of Group D * period were statistically significant ($P = 0.031$ and $P = 0.014$, respectively) in Model 1. Statistically significant differences for the interaction of Group C * period and Group D * period were also confirmed ($P = 0.05$ and $P = 0.025$, respectively) in Model 2. These results indicated that the long-term proportion of positivity varied with piercings. On the other hand, the interaction of Group B * period in Model 1 and the interaction of Group D * period in Model 3 were not significant ($P = 0.985$ and $P = 0.346$, respectively).

c) Gender and Age (Table 4 and Fig. 2)

The positive GST rate was significantly higher in females on the D7 and 1-month readings. On the D7 reading, the positive rate was significantly higher in patients with increasing age. At the 1-month reading, the positive rate also tended to be higher, depending on patient age.

Discussion

A contact allergy to gold is controversial.¹¹ Iwatsuki et al.¹² report that histologic findings of the persistence granuloma-like region caused by allergic contact dermatitis due to gold piercing appears as a pseudolymphoma. At the GST of the TRUE test application site, a late reaction, a long-lasting positive reaction, and histological pseudolymphoma-like findings have been reported.^{5,7,8,9,10} Furthermore, it has been reported that persistent positive reactions are also observed in healthy people.¹³ Although the American Society for Contact Dermatitis included gold as a core allergen in 2013,¹⁴ European countries and the North American Contact Dermatitis Group excluded gold from the baseline series.¹¹ In Japan, GST 0.5% pet has been applied together with the Japanese Baseline Series from 1994, and the positive rate of GST

0.5% pet was 2%–10% from 1994 – 2014.¹⁵ For chloroauric acid 0.2% aq., Nonaka et al.¹⁶ report that the positive rate is 8.4% in their single center study. From 2015, we have used the TRUE test as the Japanese Baseline Series.⁵ In Japan, the GST of the TRUE test positive rate exceeds 20% (Fig. 3).^{5,17} We hypothesized that this was not due to an increase in gold-sensitized cases, but to the detection of false-negative gold-sensitized cases with GST 0.5% pet. Paulsen et al.¹⁸ report an 18.5% (89/480) positive rate of the GST of the TRUE test. Therefore, the positive rate of the GST of the TRUE test was approximately 20%.

The source of sensitization to gold allergy has been reported to be due to piercings¹⁹ and dental metals.^{20,21,22} Paulsen et al.¹⁸ described that the piercing rate is 96% (64/69 cases) in female positive cases, 24% (4/17 cases) in male positive cases, while the presence of dental metal was 17% (12/69 cases) in female positive cases, and 47% (8/17 cases) in male positive cases. Thus, it was suspected that piercings in females and dental metals in males might be associated with gold sensitization. In this study, we statistically analyzed the relationship between gold sensitization, piercings and dental metals by dividing the patients into four groups. In the positive cases on the D3 and/or D7 reading, the Group D, the patients with dental metal and piercings, was significantly associated with gold positivity, but up to the 1-month reading, no significant association was observed in any group. Interestingly, the groups without dental metals (Group A and Group B) had a significantly higher proportion of the late reaction (negative at D3 and D7, and positive at 1 month) compared with the groups with dental metals (Group C and Group D).

Of the 301 patients who showed a positive reaction to GST up to the 1-month reading, 21 (7%) answered that they had neither piercing nor dental metals. Other sources of gold sensitization, for example, a stent coated with gold²² or a gold medicament, could not be determined in these 21 cases. If these 21 cases were previously sensitized to gold, the source of sensitization was unknown.

The delayed reaction to gold in patch testing is considered to be an allergic reaction in a sensitized person, not an active sensitization by a patch test.²³ Bruze et al.⁶ reports the results of GST dilution series patch tests in 10 cases with a known gold sensitization. As a result, eight cases showed a positive reaction on the D7 reading, one case on the D14 reading, and one case on the D21 reading. Iwahashi et al.¹⁰ suggest that the mechanism of delayed positive reaction to GST in sensitized gold cases may be that it takes time for the ionized gold to be absorbed, and the gold ion is not readily recognized by the immune system. In this study, 93 (17.2%) out of 538 patients that did not show a positive reaction on the D3 and D7 readings showed more than a + reaction at the 1-month reading. Thus, it is important to observe the GST of the TRUE test application site for up to 1 month.

Regarding the optimum concentration of GST, Hamann et al.⁷ performed a patch test dilution series of the GST of the TRUE test using 0.075, 0.025, 0.0083, 0.0028, and 0.00093 mg/cm² GST and GST 2% pet in 20 patients who were known to have gold allergies. They reported the optimal concentration of the GST of the TRUE test was 0.075 mg/cm². In their study, they also patch tested GST 0.5% pet in 19 patients who were known to have a gold allergy, and only 12 patients (63%) had a positive reaction. They concluded that GST 0.5% pet caused a false negative reaction in 37% of gold-sensitized patients. Therefore, the sensitivity of GST 2% pet and GST of the TRUE test 0.075 mg/cm² is considered to be higher than GST 0.5% pet. However, the reports of Bruze et al.⁶ and Hamann et al.⁷ are the studies in gold-sensitized cases. In a patch test study on healthy volunteers, 22 of 31 subjects have showed a positive reaction to GST, and those subjects do not have any skin trouble for 10 years after the study.¹³ Thus, it was suspected that GST may cause an irritant reaction. The mechanism of positivity after the D7 reading could involve the following: 1) late allergic reaction to gold in sensitized cases, 2) non-specific reaction to gold transdermally absorbed from the patch test, and 3) active sensitization to gold. As shown in Table 4, the positive rate of D3/D7 readings was significantly higher in the Group B, C and D with dental metals or piercings (29.3%, 200/683) than in the Group A without both (12.7%, 8/63). If all late reactions are allergic reactions in sensitized cases, it is expected that the 337 patients with dental metals or piercings would have a higher frequency of late reactions than the 41 without either (Table 3b). However, the frequency of late reactions was higher in the 41 cases with neither in this study. It seems that 7 out of the 41 patients, who showed positive results at the 1-month reading, were sensitized to gold by patch testing; however, it needs a follow up study to conclude whether or not they were sensitized, as indicated in a previous report¹³.

It has been reported that the gold patch test positive reaction persists for a long period and shows a granuloma histologically^{10,12}. Bowyer²⁴ investigated gold compounds for patch tests and report that positive reactions persist with sodium chlorauric acid and sodium gold thiomalate, but not with GST. Since he used GST 0.5% pet for the study, GST in higher concentrations may show similar reactions to chlorauric acid and GST. In our study, 62% (129/208) of the positive reactions on the D7 reading were still positive one month later. Such positive reaction persistence is rare with other allergens. Thus, if a positive reaction to GST is found on the D7 reading, treatment of the positive site with topical steroids is recommended.

There are various problems with the gold patch test reaction, and the clinical relevance of positive cases should be examined in the future.

Acknowledgments: We would like to thank Editage (www.editage.com) for English language editing.

Data availability statement: Any data that support the findings of this study are included within the article.

References

- 1) Fowler JF Jr. Selection of patch test materials for gold allergy. *Contact Dermatitis*. 1987;7:23-25.
- 2) Möller H, Ahnide I, Gruvberger B, Bruze M. Gold trichloride and gold sodium thiosulfate as markers of contact allergy to gold. *Contact Dermatitis*. 2005;53:80-83.
- 3) Malinauskienė L, Bruze M, Isaksson M. Patch testing with the Swedish baseline series supplemented with a textile dye mix and gold in Vilnius, Lithuania and Malmö, Sweden. *Contact Dermatitis*. 2017;77:189-190.
- 4) Sato Pharmaceutical Company Ltd, Internal Document
- 5) Suzuki K, Yagami A, Ito A, et al. Positive reactions to gold sodium thiosulfate in patch test panels (TRUE Test) in Japan: A multicentre study. *Contact Dermatitis*. 2019;80:114-117.
- 6) Bruze M, Hedman H, Björkner B, Möller H. The development and course of test reactions to gold sodium thiosulfate. *Contact Dermatitis*. 1995;33:386-391.
- 7) Hamann D, Bruze M, Fowler JF Jr, Hamann CR, Andersen KE, Hamann CP. Excipient and dose per unit area affect sensitivity when patch testing with gold sodium thiosulfate. *Dermatitis*. 2018;29:258-263.
- 8) Kosumi H, Yanagi T, Izumi K, Ito T, Shimizu H. Unusual post-patch testing erythema: a late, granulomatous, non-eczematous reaction to gold sodium thiosulphate. *J Eur Acad Dermatol Venereol*. 2018;32:e126-e127.
- 9) Shibata Y, Ohko K, Sano S. Can patch test sensitization with gold sodium thiosulfate be ruled out? - A case report. *Contact Dermatitis*. 2018;78:94-95.
- 10) Iwahashi Y, Takei H, Kasa Y, Uno H, Ohtoshi S, Nakada T. Histological and immunohistological study of late-onset reactions to gold sodium thiosulfate. *Contact Dermatitis*. 2020 May 7. doi: 10.1111/cod.13592.
- 11) Chen JK, Lampel HP. Gold contact allergy: clues and controversies. *Dermatitis*. 2015;26:69-77.
- 12) Iwatsuki K, Tagami H, Moriguchi T, Yamada M. Lymphadenoid structure induced by gold hypersensitivity. *Arch Dermatol*. 1982;118:608-611.
- 13) Andersen KE, Jensen CD. Long-lasting patch reactions to gold sodium thiosulfate occurs frequently in healthy volunteers. *Contact Dermatitis*. 2007;56:214-217.

- 14) Schalock PC, Dunnick CA, Nedorost S. American Contact Dermatitis Society Core Allergen Series. *Dermatitis*. 2013;24:7-9.
- 15) Suzuki K, Matsunaga K, Yagami A, et al. Positive rates in 2013 and 2014 of Japanese Standard Allergens 2008. *J Environ Dermatol Cutan Allergol*. 2017;3:234-247.
- 16) Nonaka H, Nakada T, Iijima M. Gold allergy in Japan. *Contact Dermatitis*. 2003;48:112-114.
- 17) Japanese Contact Dermatitis Research Group in Japanese Society for Cutaneous Immunology and Allergy: http://www.jsdacd.org/docs/useful_info/JSA_ResearchData.pdf.
- 18) Paulsen E, Andersen F, Vestergaard L, Andersen KE. Screening for gold sensitization in consecutive eczema patients: Prevalence, relevance, and sources of exposure. *Dermatitis*. 2019;30:222-226.
- 19) Nakada T, Iijima M, Nakayama H, Maibach HI. Rôle of ear piercing in metal allergic contact dermatitis. *Contact Dermatitis*. 1997;36:233-236.
- 20) Ahlgren C, Ahnlide I, Björkner B, et al. Contact allergy to gold is correlated to dental gold. *Acta Derm Venereol*. 2002;82:41-44.
- 21) Ahnlide I, Björkner B, Bruze M, et al. Exposure to metallic gold in patients with contact allergy to gold sodium thiosulfate. *Contact Dermatitis*. 2000;43:344-350.
- 22) Möller H. Contact allergy to gold as a model for clinical-experimental research. *Contact Dermatitis*. 2010; 62:193-200.
- 23) Zirwas MJ. Active sensitization. In: Fowler JF Jr, Zirwas MJ (eds). *Fisher's Contact Dermatitis*, 7th ed. Phoenix, AZ: Contact Dermatitis Institute; 2019:34-35.
- 24) Bowyer A. Epidermal reactions and prolonged dermal reactions to patch testing with gold salts. *Acta Derm Venereol*. 1967; 47:9-14.

Tables

Table 1 Clinical characteristics of the patients.

	Group A (n = 63)	Group B (n = 44)	Group C (n = 438)	Group D (n = 201)	Total (n = 746)
Piercings	No	Yes	No	Yes	
Dental metals	No	No	Yes	Yes	
Gender, n (%)					
Male	16 (25.4)	5 (11.4)	110 (25.1)	12 (6.0)	143 (19.1)
Female	47 (74.6)	39 (88.6)	328 (74.9)	189 (94.0)	603 (80.8)
Age, mean $\pm$ SD					
Male	35.5 $\pm$ 14.7	30.8 $\pm$ 8.5	53.6 $\pm$ 16.9	32.8 $\pm$ 9.9	48.9 $\pm$ 18.0
Female	39.2 $\pm$ 21.3	31.7 $\pm$ 9.5	55.1 $\pm$ 16.6	45.1 $\pm$ 13.3	49.1 $\pm$ 17.2
Disease [†] , n (%)					
Contact dermatitis	37 (58.7)	29 (65.9)	242 (55.3)	104 (51.7)	412 (55.2)
Atopic dermatitis	8 (12.7)	4 (9.1)	44 (10.0)	17 (8.5)	73 (9.8)
Metal allergy	3 (4.8)	4 (9.1)	36 (8.2)	29 (14.4)	72 (9.7)
Palmoplantar pustulosis	1 (1.6)	0	21 (4.8)	8 (4.0)	30 (4.0)
Dyshidrotic eczema	1 (1.6)	0	15 (3.4)	3 (1.5)	19 (2.5)
Lichen planus	1 (1.6)	0	14 (3.2)	2 (1.0)	17 (2.3)
Rosacea / Rosacea-like dermatitis	1 (1.6)	0	4 (1.0)	5 (2.5)	10 (1.3)
Cheilitis	2 (3.2)	0	2 (0.5)	1 (0.5)	5 (0.7)
Discomfort in the oral cavity	0	0	6 (1.4)	4 (2.0)	5 (0.7)
Other disease	9 (14.3)	7 (15.9)	54 (12.3)	28 (13.9)	103 (13.8)

[†]Diagnosed after patch testing

Table 2 Relevant patch test reactions to gold, piercings, and dental metals.

Strongest reaction [†] on D3 and D7 reading	1-month reading	Piercing	Dental metal	Total
Positive (+, ++, +++) (208 cases, M:F = 18:190)	Positive (129 cases, M:F = 9:120)	Yes	Yes	53
			No	2
		No	Yes	70
			No	4
	Negative (79 cases, M:F = 9:70)	Yes	Yes	26
			No	4
		No	Yes	45
			No	4
Not positive (?+, IR) (160 cases, M:F = 28:132)	Positive (53 cases, M:F = 7:46)	Yes	Yes	15
			No	4
		No	Yes	28
			No	6
	Negative (107 cases, M:F = 21:86)	Yes	Yes	28
			No	8
		No	Yes	63
			No	8
Negative (-) (378 cases, M:F = 97:281)	Positive (40 cases, M:F = 5:35)	Yes	Yes	6
			No	6
		No	Yes	21
			No	7
	Negative(338 cases, M:F = 92:246)	Yes	Yes	73
			No	20
		No	Yes	211
			No	34
Total				746

[†]International Contact Dermatitis Research Group criteria

M: male, F: female

Table 3a Strongest reaction[†] on D3 and D7 readings and 1-month reading

Strongest reaction [†] on D3 and D7 readings			1-month reading	
Positive 208 cases	+	147 cases	Positive	93 (63.3%)
			Negative	54
	++	55 cases	Positive	31 (56.4%)
			Negative	24
	+++	6 cases	positive	5 (83.3%)
			Negative	1
Not positive 538 cases	?+	132 cases	Positive	44 (33.3%)
			Negative	88
	IR	28 cases	Positive	9 (32.1%)
			Negative	19
	-	378 cases	Positive	40 (10.6%)
			Negative	338

[†] International Contact Dermatitis Research Group criteria

Table 3b. Relevance of 1-month reading and piercing or dental metal in 378 cases with a negative reaction on D3 and D7 readings

			1-month reading	
Negative on D3 and D7 readings 378 cases	Either piercing or dental metal	338 cases	Positive	33 cases (9.8%, 33/337)
			Negative	304 cases
	Neither piercing nor dental metal	41 cases	Positive	7 cases (17.1%, 7/41)
			Negative	34 cases

Table 4 Statistical analysis of patch test reactions to gold based on piercings, dental metals, gender, and age using logistic regression model.

	no. of cases	Reading at D3 and/or D7						Reading at 1 month					
		no. of positives	positive rates	odds ratio	95% confidence interval lower limit value	95% confidence interval upper limit value	P value	no. of positives	positive rates	odds ratio	95% confidence interval lower limit value	95% confidence interval upper limit value	P value
a) Relevance to piercings and dental metals													
(Intercept)				0.0802	0.0326	0.197	< 0.001			0.442	0.228	0.855	0.015
Group A (piercing no • dental metals no)	63	8	12.7%	—	—	—	—	21	33.3%	—	—	—	—
Group B (piercing yes • dental metals no)	44	6	13.6%	1.15	0.363	3.67	0.807	16	36.4%	1.07	0.471	2.45	0.867
Group C (piercing no • dental metals yes)	438	115	26.3%	1.87	0.841	4.17	0.125	164	37.4%	1.04	0.572	1.87	0.908
Group D (piercing yes • dental metals yes)	201	79	39.3%	3.6	1.6	8.09	0.002	100	49.8%	1.59	0.865	2.92	0.135
b) Gender													
Female	603	190	31.5%	—	—	—	—	271	44.9%	—	—	—	—
Male	143	18	12.6%	0.361	0.211	0.619	< 0.001	30	21.0%	0.359	0.231	0.56	< 0.001
c) Age													
Age	746	208	27.9%	1.02	1.01	1.03	< 0.001	301	40.3%	1.01	0.999	1.02	0.067

Table 5 Generalized estimating equations (GEE) analysis to compare the difference of proportion in gold positivity at D3 and/or D7 and up to 1 month.

	Model 1 (reference: Group A)				Model 2 (reference: Group B)				Model 3 (reference: Group C)			
	odds ratio	95% confidence interval lower limit value	95% confidence interval upper limit value	P value	odds ratio	95% confidence interval lower limit value	95% confidence interval upper limit value	P value	odds ratio	95% confidence interval lower limit value	95% confidence interval upper limit value	P value
(Intercept)	0.11	0.05	0.255	<0.001	0.13	0.056	0.306	<0.001	0.23	0.13	0.393	<0.001
Group A (piercing no • dental metals no)	-	-	-	-	0.86	0.292	2.525	0.783	0.5	0.231	1.08	0.078
Group B (piercing yes • dental metals no)	1.16	0.396	3.42	0.783	-	-	-	-	0.58	0.249	1.359	0.211
Group C (piercing no • dental metals yes)	2.00	0.926	4.322	0.078	1.72	0.736	4.016	0.211	-	-	-	-
Group D (piercing yes • dental metals yes)	3.54	1.618	7.748	0.002	3.04	1.3	7.12	0.01	1.77	1.218	2.573	0.003
1-month reading	3.53	1.87	6.669	<0.001	3.5	1.749	7.004	<0.001	1.72	1.491	1.985	<0.001
Group (A) * period (1-month reading)	-	-	-	-	1.01	0.393	2.588	0.985	2.05	1.07	3.939	0.031
Group (B) * period (1-month reading)	0.99	0.386	2.542	0.985	-	-	-	-	2.03	1.001	4.135	0.05
Group (C) * period (1-month reading)	0.49	0.254	0.935	0.031	0.49	0.242	0.999	0.05	-	-	-	-
Group (D) * period (1-month reading)	0.44	0.226	0.845	0.014	0.44	0.215	0.902	0.025	0.9	0.714	1.125	0.346
Sex (Male)	0.38	0.242	0.589	<0.001	0.38	0.242	0.589	<0.001	0.38	0.242	0.589	<0.001
Age	1.01	1.003	1.021	0.012	1.01	1.003	1.021	0.012	1.01	1.003	1.021	0.012

Figure Legends

Fig. 1 Positive ratio of gold sodium thiosulfate as a function of the presence of piercings and dental metals.

(a) Readings at D3 and/or D7. (b) Readings up to 1 month.

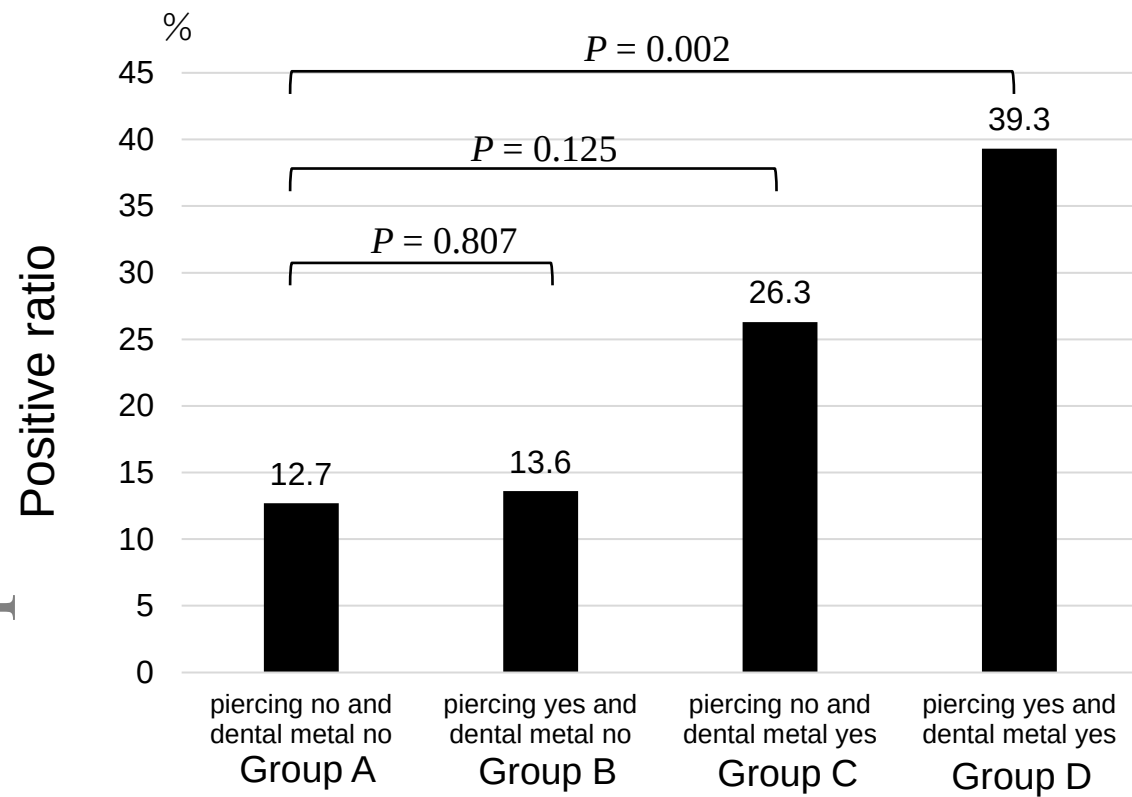
Fig. 2 Positive ratio of gold sodium thiosulfate by age.

(a) Readings at D3 and/or D7. (b) Readings up to 1 month.

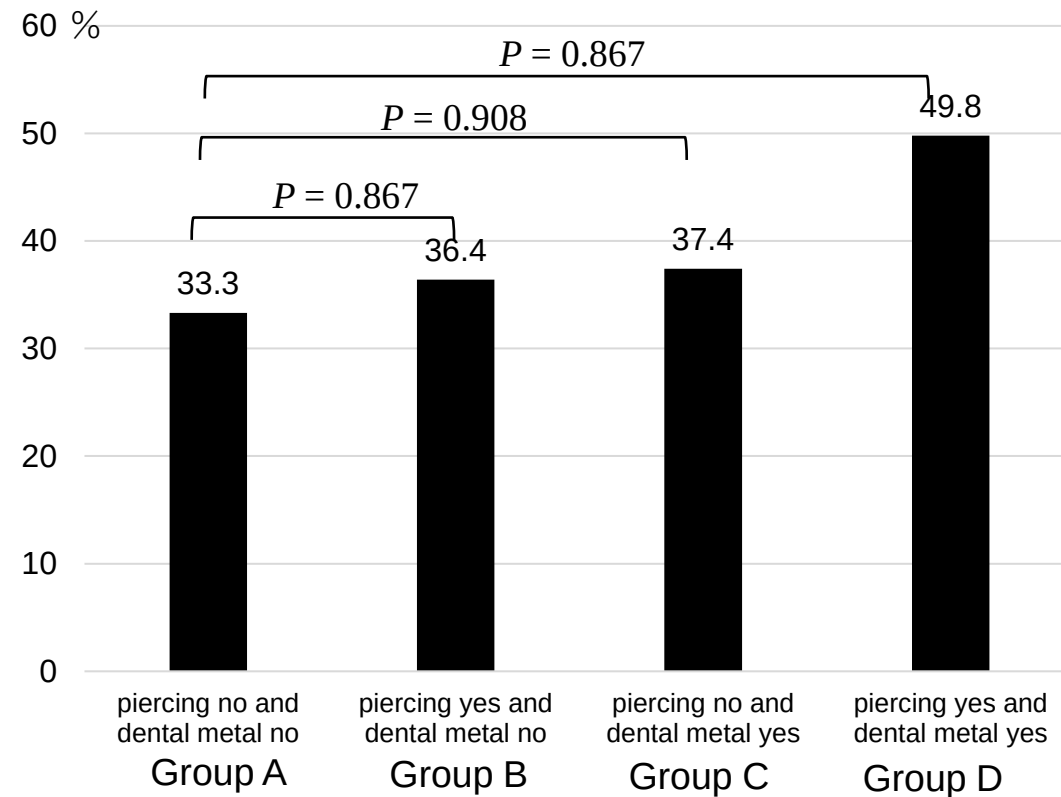
Fig. 3 Annual positive ratios of gold sodium thiosulfate (GST) in Japanese Baseline Series.

pet = petrolatum.

Fig.1

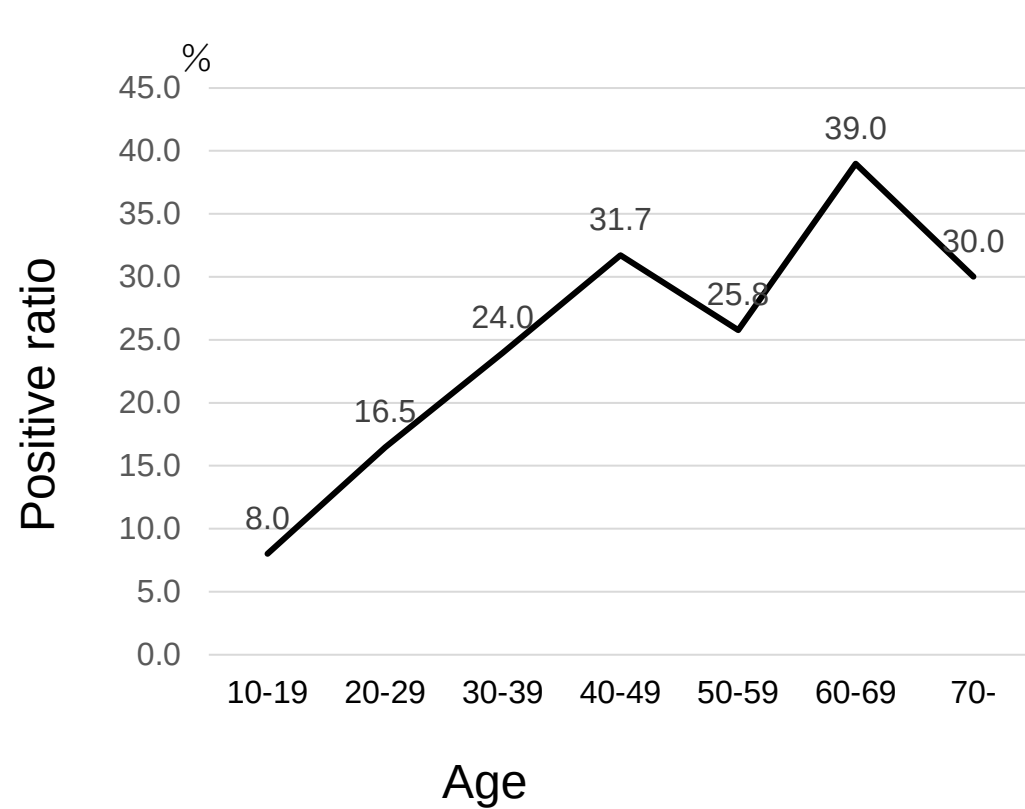


a) Readings at D3 and/or D7

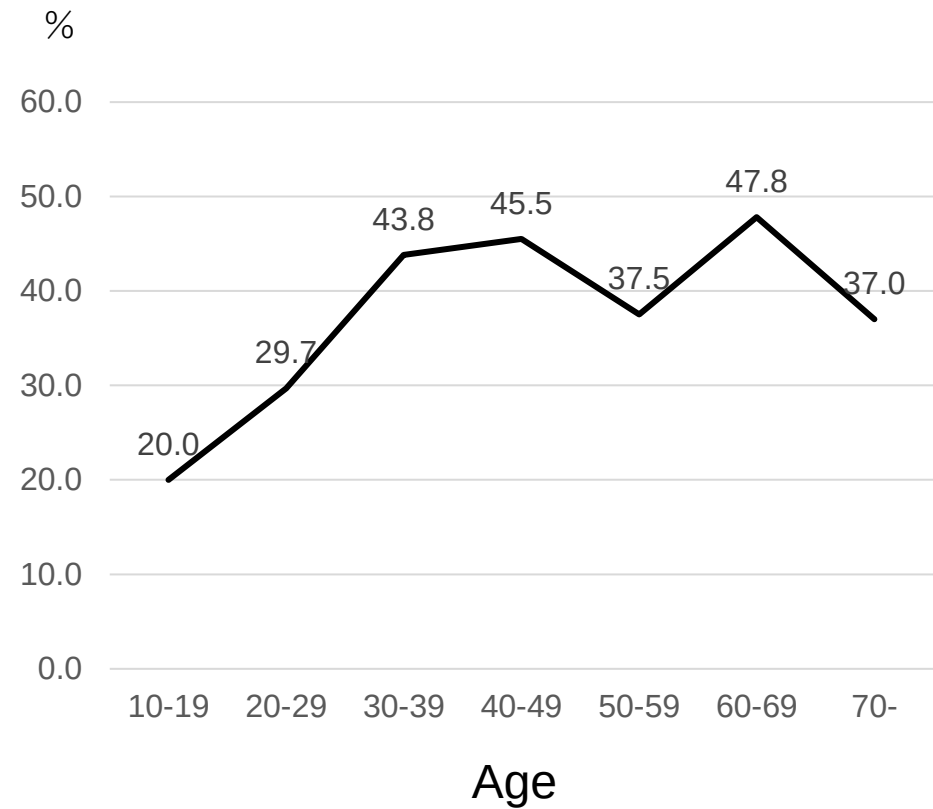


b) Reading up to 1 month

Fig. 2



a) Readings at D3 and/or D7



b) Readings up to 1 month

Fig. 3

