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The effect of a low-nickel diet and nickel sensitization on gastroesophageal reflux disease: A pilot study

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Abstract

Background/Aims—Gastroesophageal reflux disease (GERD) is a common medical condition, frequently refractory to medical therapy. Nickel is a leading cause of allergic contact dermatitis. Although nickel is widely found in foods, the effect of nickel on GERD is unknown. This pilot study sought to evaluate the effect of a low-nickel diet on GERD and determine if epicutaneous patch testing to nickel could predict responsiveness to a low-nickel diet.

Methods—This prospective, single-site pilot study recruited 20 refractory GERD patients as determined by GERD Health-Related Quality of Life (GERD-HRQL) scores. All patients had epicutaneous patch testing for nickel and were then instructed to follow a low-nickel diet for 8 weeks regardless of patch test results. GERD-HRQL was recorded at baseline and following 8 weeks of a low-nickel diet. Demographic and clinical data associated with GERD and nickel allergy were recorded. A Wilcoxon signed-rank test and nonparametric analysis of longitudinal

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Ethics statement The study was performed in accordance with the Helsinki Declaration of 1975, as revised in 2000 and 2008 concerning human rights, and the authors followed the policy concerning informed consent as shown on [Springer.com](https://www.springer.com). The study was conducted after obtaining proper ethical clearance from the institutional ethics committee.

IRB statement The study protocol was approved by the West Virginia University institutional review board.

Guarantor of the article Senior author Swapna Gayam, MD, accepts full responsibility for the conduct of the study, has had access to the data, and controls the decision to publish.

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Conflict of interest AY, RH, MM, EG, WF, RC, ZZ, and SG declare that they have no conflict of interest. All authors had access to study data and approved the final manuscript.

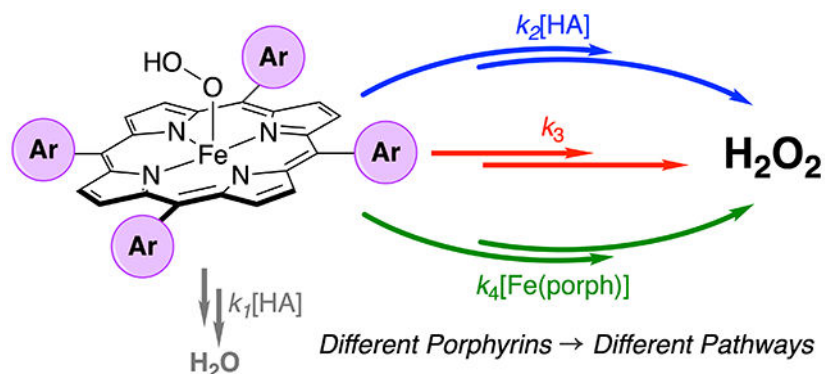
data were run to determine statistical significance in pre- and post- GERD-HRQL scores in nickel patch test–positive and negative groups.

Results—Nearly all (19/20 [95%]) participants reported reduced GERD symptoms after 8 weeks on a low-nickel diet. Mean total GERD-HRQL, regurgitation, and heartburn scores declined (27.05 ± 16.04 , 11.45 ± 6.46 , 10.85 ± 8.29). Participants with positive vs. negative patch testing to nickel responded equivalently to a low-nickel diet.

Conclusions—A low-nickel diet improves GERD symptoms, but responsiveness to a low-nickel diet does not correlate with epicutaneous patch testing to nickel.

Trial registration—[Clinicaltrials.gov](https://clinicaltrials.gov) number: [NCT03720756](https://clinicaltrials.gov/ct2/show/study/NCT03720756)

Graphical Abstract



Keywords

Dietary treatment; Esophagus; Food allergy; Gastroesophageal reflux disease; Nickel; Patch test

Introduction

The American Gastroenterological Association states that gastroesophageal reflux disease (GERD), also known as acid reflux, occurs when acid or other stomach contents back up in the esophagus. It is one of the most commonly diagnosed gastrointestinal (GI) diseases in Western countries [1]. Food allergies and sensitization of the esophageal mucosa to allergens are suspected to play a role [2]. Furthermore, there is frequent co-existence of GERD and food allergy. In infants, this can be up to 40% to 50% [3–5]. In children, GERD can cause vomiting, failure to thrive, and growth and sleep disturbances. Children with refractory GERD showed strong correlation between oral cow’s milk challenge and patch testing to cow’s milk [6]. Patch testing had 79% sensitivity and 91% specificity for cow’s milk allergy in pediatric patients with GI symptoms, predominately GERD [7]. Children with positive patch testing to cow’s milk have higher reflux index compared with patch test-negative GERD patients [8].

In adults, the common symptoms of GERD include heartburn and regurgitation following large or fatty meals. Evaluation of 65 adults with GERD on proton pump inhibitors (PPI) showed 80% improved after a 6-week restriction diet guided by patch testing. Sensitization

to foods in refractory GERD was found to be independent of PPI treatment duration [9]. Other studies have shown that patients with GERD are more likely to have nickel sensitization than matched controls [10, 11]. Thus, in both children and adults, there are multiple studies demonstrating an association between cutaneous allergy and GERD.

Nickel is a durable, silver-colored metal frequently found in objects such as jewelry. Nickel is the most common allergen detected in patch test clinics with approximately 20% of those tested reacting positively to nickel [12]. Patch test positivity to nickel is traditionally more common in women due to more prevalent piercing practices compared with men. Despite extensive literature linking nickel to allergic contact dermatitis on the skin, little is known regarding the potential of nickel-rich foods to cause allergic sensitization of the GI mucosa. On the contrary, a nickel-free diet has been shown to have beneficial effects on *Helicobacter pylori* eradication [13]. Many foods rich in nickel are associated with GERD, yet the relationship between nickel allergy and GERD remains unclear [14].

The primary objectives of this study were to determine whether those with GERD are more likely than the general population to have nickel allergy, evaluate if GERD symptoms improve following a low-nickel diet, and determine if epicutaneous patch testing for nickel could predict responsiveness to a low-nickel diet.

Methods

Participants

We prospectively enrolled patients seen at the West Virginia University Digestive Disease and Dermatology clinics between February 2019 and December 2019. Enrollment criteria included age 18 years or older with a history of GERD as diagnosed by a gastroenterologist, and confirmed symptomatic GERD at the time of initial visit as determined by a score of at least 30 on the validated GERD Health-Related Quality of Life (GERD-HRQL) questionnaire [15]. Patients actively taking a PPI must have been on the PPI for at least 3 months without resolution of GERD symptoms to be considered refractory. Patients were excluded if they had treatment with a steroid (oral or topical) or experienced sunburn within the past 4 weeks because these are known to cause false negative patch test results. Patients with prior history of patch testing were also excluded. All vulnerable populations were excluded. The study protocol was approved by the West Virginia University institutional review board.

Patch testing

Epicutaneous patch testing was performed under occlusive chamber application preferentially to the patient's upper back using a 2 × 5 panel Finn Chambers AQUA® (Smart Practice, Phoenix, Arizona, US) system secured with non-adhesive surgical tape. In total, four allergens including nickel sulfate hexahydrate, cobalt (II) chromium hexahydrate, balsam of Peru, and cinnamic aldehyde were used as test allergens (allergEAZE, Brial Allergen GmbH, Germany) along with a negative control. The additional allergens were chosen to aid in patient blinding and because they have previously been implicated in GI allergy [2]. The patch test was occluded for 48 h. All subjects were asked to photograph the

patch-tested skin after 48 and 96 h to allow two visual readings. Two board-certified dermatologists assessed patch test reactions using the established International Contact Dermatitis Research Group (ICDRG) system for clinical scoring of allergic reactions as shown in Table 1 [16]. All doubtful reactions were classified as patch test-negative reactions. Patients were blinded to patch test results until completion of the 8-week low-nickel diet (Supplementary Table 1) and the follow-up GERD-HRQL questionnaire.

GERD-HRQL scoring

The GERD-HRQL instrument, as recommended for use by the European Association for Endoscopic Surgery, assessed GERD symptoms before and after low-nickel diet implementation [17]. This questionnaire uses a numerical Likert-type response, whereby each patient assesses the severity of symptoms on an ordinal scale. The GERD-HRQL has a possible maximum score of 75 and a minimum score of 0, with the heartburn and regurgitation arms having maximum and minimum scores of 30 and 0 each. Patients returned for a follow-up appointment within 2 weeks of completion of the low-nickel diet to complete the follow-up GERD-HRQL.

Statistical analysis

Study participants who reacted positive to nickel sulfate hexahydrate were compared with participants who tested negative. Data analyses were performed using R (version 3.6.2, R development core team, Vienna, Austria). A Wilcoxon signed-rank test was conducted to determine statistical significance between GERD-HRQL score distribution before and after low-nickel diet implementation. A nonparametric analysis of the longitudinal data model was conducted, where the outcome variable was GERD-HRQL scoring and the classification factors included time and group, to determine if a significant difference existed between nickel patch test-positive and negative total GERD-HRQL, regurgitation, and heartburn scores [18]. Fisher's exact test was conducted to determine if there was a significant difference between the prevalence of nickel allergy in GERD and the general population.

Results

Demographics

The characteristics of study participants are presented in Table 2. All patients presented with a positive history of regurgitation, heartburn, and gastroesophageal reflux. The total cohort included 20 patients, 16 females and 4 males with a mean age of 49.95 ± 12.74 years. All participants were Caucasian. Smoking history was positive in 8/20 (40%) participants. The average BMI of the study participants was 35.24 ± 9.04 (Table 3).

Patch test reactions

Among the study participants, 3 (15%) had patch test positivity to nickel sulfate hexahydrate, 6 (30%) to balsam of Peru, 1 (5%) to cinnamic aldehyde, and none to cobalt (II) chloride hexahydrate. Nickel patch test reactions are shown in Table 2. The prevalence of nickel allergy in GERD was not significantly different than the known prevalence in the general population [19].

GERD-HRQL scores

At baseline, study participants reported GERD-HRQL of 48.60 ± 11.44 . Average baseline heartburn and regurgitation scores were 21.10 ± 4.25 and 19.65 ± 5.44 , respectively. Nearly all (19/20 [95%]) study participants saw marked improvement in GERD-HRQL following the implementation of a low-nickel diet. Among all participants, the mean total GERD-HRQL decreased by 27.05 ± 16.04 following low-nickel diet implementation. The mean heartburn score decreased by 11.45 ± 6.46 , and the mean regurgitation score decreased by 10.85 ± 8.29 . When comparing all study participants, a low-nickel diet significantly decreased total GERD-HRQL ($p < 0.001$), heartburn ($p < 0.001$), and regurgitation scores ($p < 0.001$).

The subset of participants with patch test positivity to nickel also had improvement with decreased mean total GERD-HRQL, heartburn, and regurgitation scores (14.67 ± 14.82 , 6.67 ± 7.59 , and 4.67 ± 7.72 , respectively), but the improvement was more modest than that of participants with patch test negativity to nickel (29.24 ± 15.23 , 12.29 ± 5.85 , and 11.94 ± 7.90 , respectively). GERD-HRQL, heartburn, and regurgitation scores following a low-nickel diet were not significantly different between those who tested positive vs. negative on patch testing to nickel. Before and after GERD-HRQL scores are shown in Fig. 1.

Satisfaction ratings

Nearly all (19/20 [95%]) participants reported dissatisfaction with GERD symptoms prior to low-nickel diet implementation, with a single participant reporting neutral feelings to GERD symptoms. Following low-nickel diet implementation, 9/20 (45%) participants changed their rating from dissatisfied to satisfied with GERD symptoms, 5/20 (25%) changed from dissatisfied to neutral, 5/20 (25%) stayed dissatisfied, and 1/20 (5%) remained neutral (Fig. 2).

Discussion

Nickel, a metal commonly found in jewelry and other environmental products, is the most common allergen to elicit a positive response on patch testing. Nickel is a well-known cause of allergic contact dermatitis, classically appearing on the earlobes from earrings and near the umbilicus from contact with belt buckles. Ingestion of nickel-rich food products such as cocoa, chocolate, legumes, cereals, and canned foods has been shown to flare dermatitis in nickel-sensitive patients. Likewise, nickel ingestion in foods can cause similar inflammatory reactions in the intestinal mucosa [20]. Thus, dietary consumption of nickel has documented inflammatory effects on the cutaneous and GI epithelium.

GERD is one of the most common medical conditions requiring clinical care. Response to available therapy is frequently unsatisfactory resulting in a specialist referral [21]. Additional treatment options for GERD are warranted, especially diet-based approaches rather than pharmacotherapy. Patch test-guided dietary restriction in GERD has previously been shown to be helpful. This study is the first to examine the effect of a low-nickel diet on GERD symptoms and the first to determine if epicutaneous patch testing to nickel could predict responsiveness to a low-nickel diet.

Low-nickel diet decreased GERD symptom severity in both heartburn and regurgitation in 19/20 (95%) participants and led 14/20 (70%) participants to improve satisfaction ratings pertaining to GERD symptoms. This striking improvement in GERD symptomatology is noteworthy, particularly given high participant satisfaction with results. When asked about changes in GERD symptoms, most participants acknowledged significant improvement, some planning to continue the low-nickel diet due to complete resolution of GERD. Strengths of the study include 100% study completion rate among participants, with 80% (16/20) of participants finding the low-nickel diet tolerable over the 8-week study period. Also, participants and study coordinators were blinded to patch test results until completion of the 8-week low-nickel diet. Limitations of the study include lack of a dietary placebo (i.e. all 20 participants followed the same diet) and small sample size which limited the ability to detect small variations in GERD symptomatology between nickel positive vs. nickel negative participants. Also, participants without a positive patch test reaction may have determined their patch test was negative thereby introducing bias. Furthermore, participants lost 0.3 kg on average after the 8-week intervention, and dietary restriction alone may have led to the improvement in GERD symptoms. Since all participants were Caucasian, these results may not be generalizable to all populations. Finally, some participants may have had alternative diagnoses other than GERD, such as eosinophilic esophagitis.

In conclusion, a low-nickel diet over an 8-week period leads to a marked reduction in GERD symptomatology in 95% of participants. All participants completed the 8-week period of dietary restriction without dropout noting the limited adverse effect on quality of life. Epicutaneous patch testing for nickel was unable to predict responsiveness of GERD symptomatology to a low-nickel diet. Further studies with larger sample size and placebo-controlled dietary intervention are needed to validate these findings. The authors are hopeful this pilot study will stimulate future prospective, randomized clinical trials evaluating the effect of a low-nickel diet in GERD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Bullet points of the study highlights**What is already known?**

- Nickel sensitization is more prevalent in gastroesophageal reflux disease (GERD) patients.
- The effect of a low nickel diet on GERD symptoms has not been explored.

What is new in this study?

- Among 20 participants placed on a low nickel diet, nearly all (19/20) participants reported reduced GERD symptoms after 8 weeks.
- Participants with positive vs. negative patch testing to nickel responded equivalently to a low nickel diet.

What are the future clinical and research implications of the study findings?

- A low nickel diet reduces GERD symptoms, regardless of nickel sensitization.

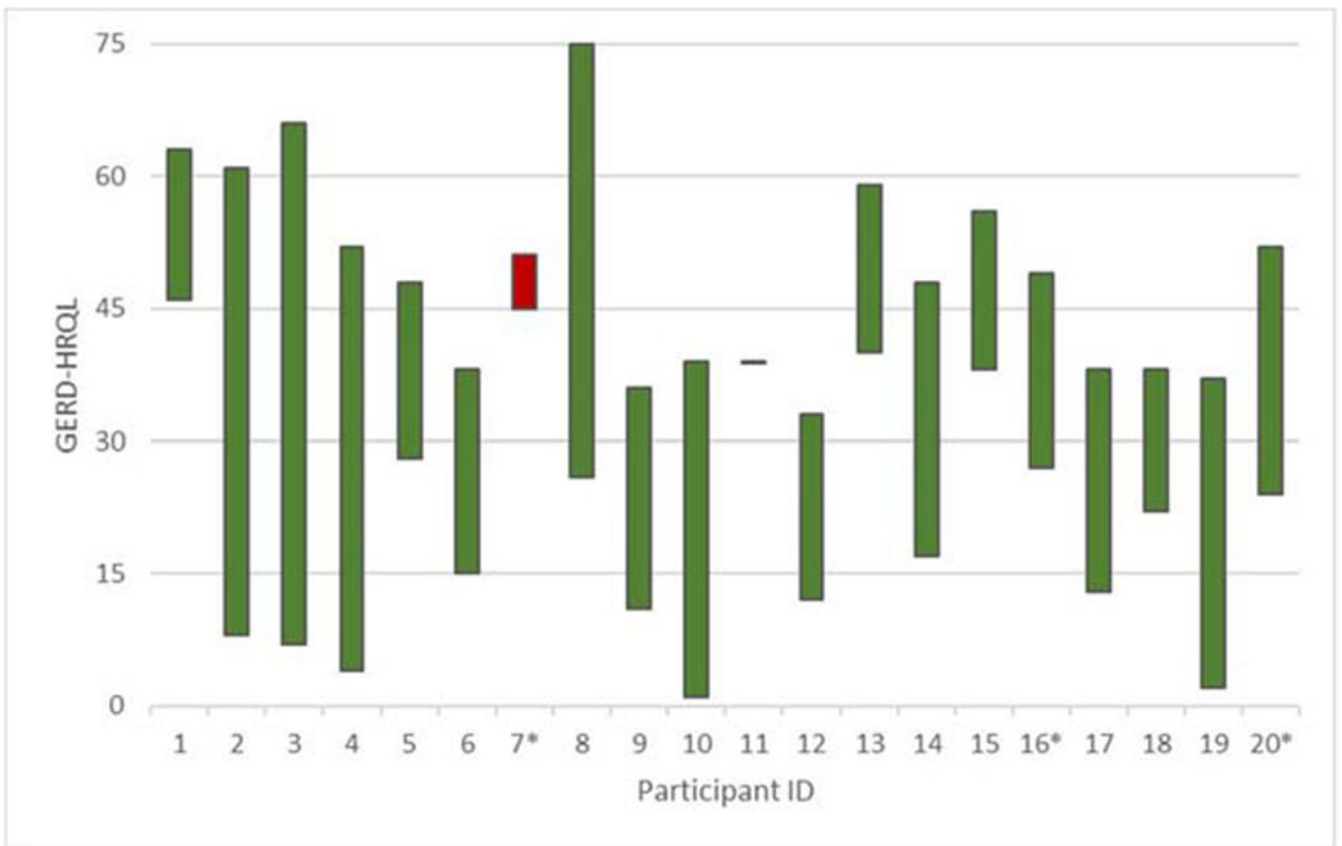


Fig. 1. GERD-HRQL score change following low-nickel diet implementation. A candlestick chart depicts the change in GERD-HRQL scores of study participants who completed the 8-week low-nickel diet. A decline in GERD symptom severity is noted in green, while worsening symptom severity is noted in red. Asterisk indicates nickel allergy positive–participants with at least 1+ on patch testing according to ICDRG criteria. *GERD* gastroesophageal reflux disease, *HRQL* health-related quality of life, ICDRG International contact dermatitis research group

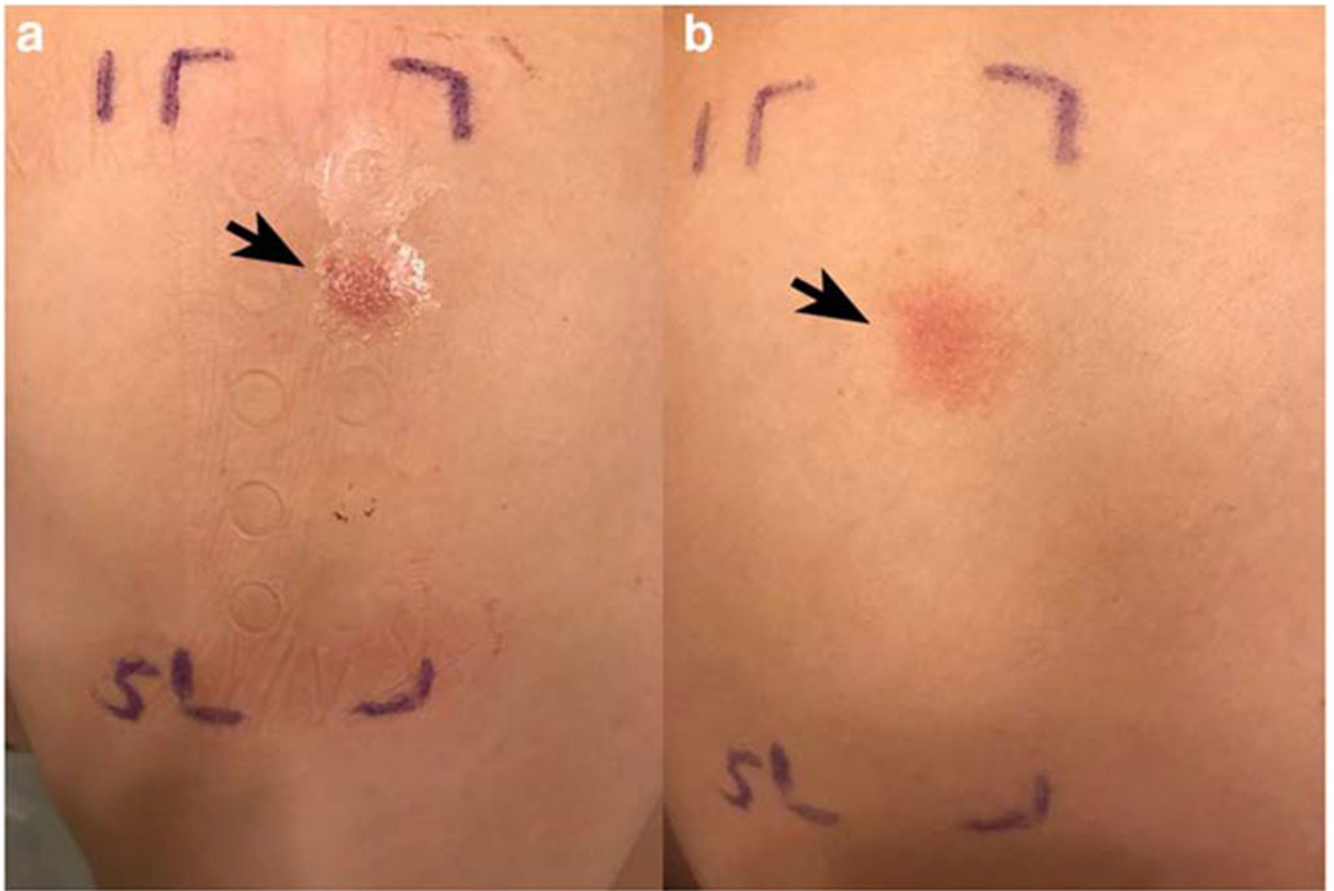


Fig. 2. Weak positive reaction at 48 and 96 h. **a** At 48 h, palpable erythema (arrow) is noted on the upper back located at the site of nickel sulfate hexahydrate Finn Chambers AQUA® (Smart Practice, Phoenix, Arizona, US) system occlusion. **b** At 96 h, the erythema and infiltration (arrow) have spread to all skin contacted by nickel sulfate hexahydrate. According to International contact dermatitis research group criteria, this patch test was read as 1+

International Contact Dermatitis Research Group patch test scaling recommendations

Table 1

Symbol	Morphology	Interpretation
-	No reaction	Negative
?+	Non-palpable, faint erythema	Doubtful reaction
1+	Erythema, infiltration, possibly discrete papules	Weak positive
2+	Erythema, infiltration, papules, vesicles	Strong positive
3+	Erythema, infiltration, confluent vesicles	Extreme positive
ir	Different types of reactions (blisters, soap effect)	Irritant reaction

Table 2

Baseline characteristics of GERD patients. *GERD* gastroesophageal reflux disease, *HRQL* health-related quality of life, *BMI* body mass index

Characteristic	Number (%) [*]
Age, mean \pm SD, years	49.95 \pm 12.74
Gender	
Female	16 (80)
Male	4 (20)
Race	
White	20 (100)
Non-white	0 (0)
Smoking history	
Yes	8 (40)
No	12 (60)
Asthma	
Yes	12 (60)
No	8 (40)
BMI, mean \pm SD	35.24 \pm 9.04
Baseline GERD-HRQL, mean \pm SD	48.60 \pm 11.44
GERD satisfaction rating	
Satisfied	0 (0)
Neutral	1 (5)
Dissatisfied	19 (95)

^{*} Unless otherwise specified

Patch test reactions and GERD-HRQL scores. GERD gastroesophageal reflux disease, HRQL health-related quality of life

Table 3

Participant ID	Nickel patch test reactions	Baseline GERD-HRQL	Follow-up GERD-HRQL	Follow-up GERD satisfaction rating
1	-	63	46	Dissatisfied
2	-	61	8	Satisfied
3	-	66	7	Satisfied
4	-	52	4	Satisfied
5	-	48	28	Neutral
6	?+	38	15	Neutral
7*	2+	45	51	Dissatisfied
8	-	75	26	Satisfied
9	?+	36	11	Neutral
10	-	39	1	Satisfied
11	-	39	39	Dissatisfied
12	-	33	12	Neutral
13	-	59	40	Neutral
14	-	48	17	Neutral
15	-	56	38	Dissatisfied
16*	1+	49	27	Dissatisfied
17	-	38	13	Satisfied
18	-	38	22	Satisfied
19	-	37	2	Satisfied
20*	2+	52	24	Satisfied

* Nickel allergy–positive participants with at least 1+ on patch testing according to International Contact Dermatitis Research Group criteria