Nickel Sensitivity in Patients With Irritable Bowel Syndrome

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Research Article

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Abstract

**Aim:** Irritable bowel syndrome (IBS) is a gastrointestinal disorder characterized by changes in chronic abdominal pain and bowel habits, without any organic cause. Nickel is the most common contact allergen in the population. So, in our study, we aimed to investigate whether there is a relationship between nickel sensitivity and IBS.

**Methods:** This study was conducted with 50 patients with irritable bowel syndrome who were followed up in the gastroenterology department of Derince Training and Research Hospital between March 2018 and July 2018, and 40 healthy people as a control group in a single center with a dermatology department. European standard contact allergen series nickel preparate and corticosteroid pomace were applied to the back region of the study subjects. The evaluation was performed at 48, 72 and 96 hours according to the scheme proposed by the International Contact Dermatitis Research Group (ICDRG). Those who reacted at 72 hours were considered to have nickel allergy.

**Results:** The female/male ratio was 24/26 and 18/22 in the patient and control groups, respectively. The mean ages of the patient and control groups were 42.82 (±10.66) and 39.78 (±11.21) years, respectively. Nickel sensitivity was present in 38% of the patient group and 17.5% of the control group. The difference was statistically significant (p = 0.03).

**Conclusion:** We believe that the presence of nickel sensitivity is important in the pathogenesis of IBS disease. In our study, nickel sensitivity was found to be quite high in IBS patients compared to the normal population.

Introduction

Irritable bowel syndrome (IBS) is a gastrointestinal disorder characterized by alterations in bowel habits, and involves chronic abdominal pain without any organic cause. IBS, which is the most commonly diagnosed gastrointestinal disorder, has variations geographically and comprises 10% of all attendances with gastroenterologists [1]. While the prevalence of IBS was 10–15% in North America, it was 11.5% in Europe [2, 3]. The prevalence in Asian countries (between 0.8–14%) is generally lower than European countries [4, 5].

Several symptom-based criteria were recommended to standardize the diagnosis of IBS due to the lack of biological markers. The Rome IV criteria is the most used among the criteria. The presence of two of the following three criteria in a patient, including the presence of recurrent abdominal pain at least one day per week over at least 6 months, establishes the diagnosis of IBS: 1) related to defecation (relief), 2) involving changes in the frequency of defecation, and 3) changes of the appearance of feces [6].

IBS is believed to be a multifactorial disease but the etiology is not fully illuminated despite the fact that many studies about IBS exist. Conservative views about the cause of IBS include alterations in gastrointestinal motility and visceral hypersensitivity. Recent research suggests that inflammation,
alterations in fecal microflora and bacterial overgrowth play roles in the etiology. Whether there is food sensitivity and genetic predisposition are also investigated [7]. Various pathophysiological factors may coexist in the same patient. This may help to explain the complexity of IBS and the changing response to symptom-based therapies [8]. It is also accepted that psychological stress exacerbates IBS symptoms and that psychiatric comorbidity associated with it adversely affects patient status [9].

The role of foods in the pathophysiology of IBS is not clear. Some patients with IBS reported that symptoms worsened after eating. Accordingly, it is thought that intolerance develops against some foods. Factors contributing to food sensitivity were investigated in IBS patients and studies focused on food-specific antibodies, carbohydrate malabsorption and gluten sensitivity [10]. In the studies, the rate of positivity in food skin-prick tests of IBS patients was higher than in healthy individuals [11]. In other studies on this subject, IBS patients with elevated IgG titers associated with some foods were shown to reduced gastrointestinal symptoms when these foods were removed from the diet [12]. The role of diet in the management of patients with IBS requires further investigation.

Nickel is one of the most common causes of contact allergy in the community. The rate of Ni sensitivity in Turkish population was found to be 12–24% [13, 14]. Ni, a metal, can be incorporated into chemical compounds and alloys. People are often exposed to nickel through the skin. However, nickel is taken into the body by breathing, drinking water and consuming some foods [15]. Only 1 to 10% of dietary Ni is absorbed [16].

The most important source of Ni in the body is the dietary intake of foods containing high amounts of Ni. The foods containing high amounts of Ni are foods cooked in stainless steel, green vegetables, tea, tomatoes, beans, peas, spinach, onions, mushrooms, pears, wheat, corn, cereal flours, chocolate, herring, asparagus, oysters and canned foods (Table 1) [17, 18].

Table 1

<table>
<thead>
<tr>
<th>Food</th>
<th>Amount</th>
<th>Food</th>
<th>Amount</th>
<th>Food</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grain</td>
<td>0.17</td>
<td>Green vegetables</td>
<td>0.11</td>
<td>Milk</td>
<td>&lt; 0.02</td>
</tr>
<tr>
<td>Meat</td>
<td>0.04</td>
<td>Other vegetables</td>
<td>0.09</td>
<td>Hazelnut</td>
<td>2.5</td>
</tr>
<tr>
<td>Poultry</td>
<td>0.04</td>
<td>Potato</td>
<td>0.10</td>
<td>Oil</td>
<td>0.03</td>
</tr>
<tr>
<td>Fish</td>
<td>0.08</td>
<td>Egg</td>
<td>0.03</td>
<td>Fresh fruit</td>
<td>0.03</td>
</tr>
</tbody>
</table>

In a sensitive person, dermatitis may occur after adequate intake of Ni. It was found that not only contact, but also the oral administration of nickel sulfate (600-5,600 µg in a single dose) may cause eczema [19]. There are studies suggesting that Ni that induces contact dermatitis may also be associated with gastrointestinal diseases [20]. However, there are very few studies examining the relationship between Ni and IBS [21]. If such a coexistence exists, it is thought that the symptoms of patients can be improved.
and the cost of treatment may be reduced after poor diet. In this study, we aimed to investigate whether there is a relationship between IBS and Ni sensitivity.

**Methods**

This study was conducted with 50 patients over the age of 18 and 40 healthy volunteers. Between March-July 2018, 50 patients who were diagnosed with IBS according to the Rome 4 criteria, followed up in the gastroenterology clinic, who did not use any systemic medication and have dietary restrictions were included in the study. Forty healthy volunteers, who were on a similar diet, had similar ages, and no skin or systemic disease were also included in the study. Informed consent was obtained from all individual participants included in the study.

Fifty people with IBS diagnosis who participated in the study were not differentiated in terms of constipation-dominant IBS, diarrhea-dominant IBS and pain-dominant IBS.

In our study, the patients had nickel used in the European standard contact allergen series (Chemotechnique diagnostic, European baseline S-1000) and corticosteroid pomade was applied as control in the back region. The evaluation was done according to the scheme proposed by the International Contact Dermatitis Research Group (ICDRG) after 48, 72 and 96 hours, and the subjects with positive and negative reactions were recorded. Detection of nickel sensitivity was evaluated by a dermatologist.

In our study, the subjects who used topical corticosteroids for 1 week before, volunteers using systemic corticosteroids, immunosuppressive and cytotoxic treatment for at least 3 weeks before, subjects using nonsteroidal anti-inflammatory and antihistaminic drugs and pregnant women were excluded.

Individuals who wore jewelry containing nickel in the last 1 month were excluded from the study. Subjects were tested for nickel susceptibility only.

The data about people included in the patient and control groups like age, sex, occupation, hobbies, family history, duration of disease, history of allergic sensitivity were investigated and recorded on the forms prepared. The patients were warned not to take any baths, to avoid activities that would cause excessive sweating and not to use drugs that would cause mistaken evaluations of the test. Reactions that were positive at the 48th hour and negative or decreased at 72 hours were accepted as irritant. The study was approved by the local ethics committee (Kocaeli Üniversitesi Klinik Araştırmalar Etik Kurulu 2018/93, 20/02/2018).

For the statistical evaluation of the data, Statistical Package for Social Sciences (SPSS) 17 package program was used. The patch test reactions of the two groups were compared with the chi-square test and p value less than 0.05 was considered significant.

**Results**
There were 50 subjects in the patient group and 40 in the control group. The female / male ratio was 24/26 and 18/22 in the patient and control groups, respectively. The mean age of the patient and control groups were 42.82 (± 10.66) and 39.78 (± 11.21) years, respectively. Both groups were statistically similar in terms of age and gender distribution (Table 2).

| Demographic characteristics of patients and control groups and nickel sensitivity rates |
|------------------------------------------|-----------------|-----------------|-----------------|
|                                | Patient         | Control         | p-value |
| Age (mean ± SS)                  | 42.82 ± 10.66   | 39.78 ± 11.21   | 0.19    |
| Gender (f/m)                      | 24/26           | 18/22           | 0.77    |
| Nickel sensitivity (%)            | 38              | 17.5            | 0.03    |

In our study, positive results were compared in terms of gender distribution in the patient and control groups. Female dominance was found in both groups. Of the patients with positive Ni sensitization, 55% were female and 71.4% of the control group with positive nickel sensitization were female. The difference was not statistically significant. When the distribution of nickel sensitivity according to gender was examined in patients with IBS, the rate of positivity was found to be 45.8% in female patients and 34.6% in male patients, but no significant difference was found between them.

Nickel sensitivity of the patient group was 38% and the sensitivity of the control group was 17.5%. The difference between them was statistically significant (p = 0.03).

When men and women were evaluated separately, nickel sensitivity was positive in 11 women (45.8%) in the patient group and 5 women (27.7%) in the control group. But nickel sensitivity was positive in 9 men (34.6%) in the patient group, and 2 men (9.09%) in the control group (Table 3, Table 4).

| Nickel sensitivity rates between patient and control groups in women |
|----------------------------------------------------------|-----------------|-----------------|-----------------|
|                                                           | Women           | Negative        | Positive        | Total |
| Patient                                                  | 13              | 11              | 24              |
| Control                                                  | 13              | 5               | 18              |
| Total                                                    | 26              | 16              | 42              |
There was no significant difference between males and females in terms of nickel sensitivity. There was no difference between women of the patient group and control group in terms of nickel sensitivity. However, there was a higher rate of nickel sensitivity in men in the patient group than in the control group, which was significant (p = 0.03).

No volunteer had allergic reactions due to corticosteroids. Irritant reactions were not observed in both groups. But mild erythema that occurred in patients was evaluated as suspicious and negative.

**Discussion**

Nickel, which can be found everywhere in the environment, is an element that can be taken into the body through diet, breathing, touching, etc. A recent study reported that IBS-like symptoms can be seen in people eating Ni-rich foods [22].

Nickel allergy is the most common metal allergy. In parallel to that, a study by Lu et al. also reported that the most common metal allergen in patients who underwent a patch test was also Ni [23]. Nickel sensitivity in the Turkish population was reported as 12–24% [13, 14, 24]. In our study, the results for control group were consistent with the literature.

In our study, the nickel sensitivity of the patient group was determined as 38% and the sensitivity of the control group was 17.5%. Ni sensitivity was significantly higher in the patient group. In a study published by Rizzi et al. in 2017, nickel susceptibility was higher in IBS patients compared to the healthy population and symptoms improved with a low nickel diet. These findings lead researchers to develop hypotheses related to pathophysiological mechanisms linking IBS with nickel susceptibility [21].

In our study, the sensitivity of Ni in patients with IBS was significantly higher than in healthy individuals and this result is similar to the data of Rizzi et al. The results of our study, which included 50 subjects, supports the study by Rizzi et al. [21] that included 20 patients.

In our study, Ni sensitivity was detected in 10 (37.03%) of 27 patients with IBS diagnosis for less than 1 year. However, nickel sensitivity was found in 10 (43.4%) of 23 patients with IBS diagnosis for more than 1 year. Nickel sensitivity was higher in patients with longer disease duration, but the difference between the two groups was not statistically significant.

<table>
<thead>
<tr>
<th>Men</th>
<th>Negative</th>
<th>Positive</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
<td>17</td>
<td>9</td>
<td>26</td>
</tr>
<tr>
<td>Control</td>
<td>20</td>
<td>2</td>
<td>22</td>
</tr>
<tr>
<td>Total</td>
<td>37</td>
<td>11</td>
<td>48</td>
</tr>
</tbody>
</table>
There were more IBS cases in women than men. The factors like women’s more frequent referral to the doctor as a result of cultural differences, being more sensitive to psychological stress, and differences in sexes in serotonin synthesis in the central nervous system may cause IBS to be seen more frequently in women than men [25].

Nickel sensitization affected men due to more occupational exposure in the past. However, nickel sensitivity has begun to be seen more in women, especially at younger ages, because of increasing use of imitation jewelry [26].

It is known that dietary Ni may be responsible for gastrointestinal symptoms that mimic the clinical features of IBS [27]. Worsening of postprandial symptoms and lack of toleration to foods are common in IBS disease [28]. The British Association of Dietitians stated that diet and lifestyle changes should be routinely offered to IBS patients [29]. The correction of symptoms in IBS usually takes a long time. In order to achieve a significant improvement, a period of 6 months or longer is often required. Patience is very important in resolving this problem. The combination of appropriate diets and medicines is of great importance in the treatment of IBS. Foods that increase complaints should be consumed less or removed from the diet.

As a result of this study, it is thought that dietary Ni intake may have a role in the etiology of IBS. We found nickel sensitivity to be significant in our study and we think that when nickel-containing compounds are excluded from the diet of IBS patients, symptoms may be reduced. There are still few studies about this subject, and new studies involving more patients are needed.

Declarations

Ethics Approval

The study was approved by the local ethics committee (Kocaeli Üniversitesi Klinik Araştırmalar Etik Kurulu 2018/93, 20/02/2018).

Consent to Participate

Informed consent was obtained from all individual participants included in the study.

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Conflict of Interest

There is no conflict of interest with all of the authors.

Author Contributions
All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Umut Polat, Muhammed Kaya and Mesut Sezikli. The first draft of the manuscript was written by Süleyman Coşgun and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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