Titanium Hypersensitivity: A Clinical Study

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ABSTRACT
Titanium implants are extensively used to replace the missing natural teeth in prosthodontics. However, allergic reactions to titanium in dentistry has not received its due attention. Literature reports sensitivity to titanium ranging from 0.6 to 5% of the general population. The allergic reactions in patients who are sensitive to titanium ranges from type I to IV with symptoms ranging from vague pain, skin rashes to implant failure. The aim of this study was to evaluate the presence of titanium allergy by anamnesis and examination of subjects using titanium dioxide 0.5% in patch test methodology. A sample size of four hundred healthy subjects with no previous history of immunosuppression were included. Titanium dioxide 0.5% concentration in petrolatum was used to conduct the patch test. A history of allergy to any other allergen was recorded as a part of the study. Under the limitations of this study, it was concluded that, titanium can induce hypersensitivity response in susceptible patients. From this study it was observed that the hypersensitivity reactions to titanium was 0.3% in all the subjects tested. It was also observed that the individuals with a prior history of allergy to other known allergens were more susceptible to allergic reactions to titanium. Limitations of the study was the absence of a wider age group of population for this study. Future research is recommended by considering a wider age group of population and a long-term follow-up of patients.

Keywords: Titanium patch test, Dental implants, Titanium allergy.

INTRODUCTION
Titanium implants are extensively used to replace the missing natural teeth in prosthodontics, as it is one of the most biocompatible materials. The placement of any material in the body creates an interface which will be a site of dynamic interactions between the material and the body, through which the material may alter the body and vice versa.1 Despite titanium being one of the most biocompatible materials, it can still cause an allergic reaction in a small percentage of population.1

The review of literature did not reveal reports of any studies undertaken to determine sensitivity to titanium using patch test and hence present study was undertaken to determine the incidence of sensitivity to titanium in the local population.2

The study was conducted using patch test methodology employing 0.5% titanium dioxide in petrolatum base. The results were also compared between the group of subjects who gave a history of allergy to other common metal allergens such as nickel and the group of individuals who did not have any previous history of allergy.

MATERIALS AND METHODS

Materials
1. Four hundred healthy volunteers as subjects who met the criteria of inclusion and agreed to take part in this study, after being explained the study methodology, its importance and possible adverse reactions.
2. Test allergen composed of titanium dioxide 0.5% in petrolatum base.

The inclusion criteria were:
1. Individual volunteers in the age group of 18 to 60 years with no history of any systemic diseases.
2. Individual volunteers with known prior history of allergy to known metal allergens.

The exclusion criteria were:
1. Subjects suffering from any illness.
2. Subjects under immunosuppressant therapy such as corticosteroids, antihistamines, etc.

Methods
A clearance was taken from the institution’s ethical committee in compliance with the WMA declaration of Helsinki- ethical principles for medical research involving human subjects. An examiner, who was blinded regarding the purpose of the study, was trained to observe and evaluate the possible reactions, both positive and negative in the test
The study included four hundred volunteer subjects as presented in Table 1. The results of this study are presented in Table 2. A total of 11 (3%) subjects out of the 400 subjects included in this study tested positive to the patch test for titanium dioxide, of which 9 (9.09%) had a prior history of allergy to known allergens and 2 (0.66%) had not reported any past history of allergic reactions.

The difference in proportion of positive results with samples having previous history of allergy and those without having previous history of allergy was found to be statistically significant (p < 0.01).

DISCUSSION

Titanium has been considered as the material of choice in prosthodontics and implantology due to its high biocompatibility, which is primarily due to the formation of a stable oxide film. Nevertheless, sporadic cases of intolerance have been reported, in which a group of patients suffer from repeated failure with titanium implants with no known cause coming forth.3

Hypersensitivity to metals has been reported to be about 3% in the population. Based on this information, a sample size of four hundred subjects was considered to draw statistically significant results. Of the total number of subjects tested, an incidence of 3% was found for allergic reactions to titanium, which confirms to the prevalence of allergic reactions to metals in general population.4 The allergic reaction to metals in subjects who had a previous history of allergic reaction to other metals was found to be 9%, which is slightly higher than the other studies, where a prevalence of 5% have been reported. 0.66% of the individuals who did not give any prior history of allergy tested positive to titanium dioxide.5 Past literature reports have suggested a general prevalence of around 0.6% in general population and around 5% in subjects who had a history of allergic reactions to metals.6 From these results it may be concluded that titanium appears to be biocompatible to most patients, but a small subgroup of individuals may be capable of developing clinically significant hypersensitivity reactions. It was observed that the individuals having a prior history of allergy were more susceptible to allergic reaction to titanium.7

Hence, it becomes imperative to test patients who give a prior history of metal allergy to be subjected to testing for titanium hypersensitivity before treating them with end osseous implants.

Table 1: Gender distribution in the study sample

<table>
<thead>
<tr>
<th>Gender</th>
<th>n</th>
<th>%</th>
</tr>
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<tbody>
<tr>
<td>Male</td>
<td>172</td>
<td>43</td>
</tr>
<tr>
<td>Female</td>
<td>228</td>
<td>57</td>
</tr>
<tr>
<td>Total</td>
<td>400</td>
<td>100</td>
</tr>
</tbody>
</table>

Table 2: Positive results in patients (z-test for proportions)

<table>
<thead>
<tr>
<th>Positive results in patients</th>
<th>n</th>
<th>%</th>
<th>Difference in proportion</th>
<th>z</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>With h/o allergy (n = 99)</td>
<td>9</td>
<td>9.09</td>
<td>0.084</td>
<td>2.880</td>
<td>0.004</td>
</tr>
<tr>
<td>Without h/o allergy (n = 301)</td>
<td>2</td>
<td>0.66</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Total (n = 400)</td>
<td>11</td>
<td>3</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

n: Number of subjects who tested positive to an allergic reaction to titanium; The difference in proportion of positive results with samples having previous history of allergy and those without having previous history of allergy was found to be statistically significant (p < 0.01)
This study was not designed to check for hypersensitivity in patients, who are chronically exposed to titanium, though literature suggests an increased probability of allergic reaction in such patients as they would be sensitized to the allergen.\(^8\)

A review of the reports of allergic reactions to metallic implants and devices would present that they are quite common,\(^9,10\) however, literature reports on titanium hypersensitivity in oral cavity has been scarce. It may be suggested that oral-implant-related titanium hypersensitivity may be underreported due to poor understanding or failure to investigate this as a potential etiological factor. Titanium hypersensitivity as one of the factors responsible for implant failure, has been investigated and it has been found by the authors as one of the factors which may play a critical role in the failure of implants.\(^11\)

Escape of titanium particles from the implant surface toward more distal peri-implant tissues has also been reported.\(^8\) It has been suggested that fine particles may be transported by phagocytes to the regional lymph nodes, where they could be found without any signs of inflammation or foreign body reactions.\(^11\) In past, such have been considered to be of little or no biological importance.

Even though allergy to titanium has been reported, the patch test reagent for titanium had not been standardized so far. In the past when a patient was suspected to have allergic reaction to titanium, a piece of the transplanted or implanted material was left in contact with the skin of the patient to be observed periodically for signs of allergic reaction.\(^12-14\)

A reagent which was composed of pure titanium powder in a petrolatum base has been found unacceptable in the past, as it had acted like a stimulant.\(^15\) Since titanium is almost universally present in the form of titanium dioxide due to its highly reactive nature leading to the almost instantaneous formation of an oxide layer, it was suggested to use titanium dioxide instead of pure titanium.\(^16\) Using a petrolatum base allows us to deliver titanium dioxide epicutaneously, in a noninvasive method to observe for signs of allergic reactions that may develop in susceptible patients.\(^17,18\)

It may be advisable to conduct a noninvasive patch test especially in patients with a prior history of allergy to other known metallic allergens.\(^19,20\)

A difference may be suggested on the behavior of an allergen on intraoral application and in epicutaneous testing, but then again patch testing has been proven to be universally acceptable to check for suspected allergic reactions and it may be advisable to conduct a noninvasive patch test whenever in doubt before proceeding with other invasive procedures.

Limitations of this study were:

1. This study was not designed to check for hypersensitivity in patients, who are chronically exposed to titanium.
2. Long-term clinical follow-up of the patients following placement of titanium implants was not done.
3. Alternatives to titanium implants in subjects susceptible to titanium hypersensitivity could not be explored.
4. Difference in epicutaneous testing and intraoral applications.

Authors recommend future studies to encompass the limitations of this study and to further explore the possibility of hypersensitivity to titanium and its effect on the prognosis of osseointegrated titanium implants used for oral rehabilitation.

**CONCLUSION**

Under the limitations of this study, it can be concluded that, titanium can induce hypersensitivity response in a group of susceptible patients.

Of the total number of subjects tested, 3% of the subjects were found to have hypersensitivity reactions to titanium. It was observed that the individuals reporting a prior history of allergy to various known allergens were more susceptible to presenting with an allergic reaction to titanium. It may be advisable to conduct a noninvasive patch test especially in patients with a prior history of allergy to other known metallic allergens. If a patient is conclusively proven to be susceptible for an allergic reaction to titanium, other means of treatment should be explored.

**REFERENCES**


