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Original Article

Orthopedic implant hypersensitivity: Characterization of clinical presentation and effects of photobiomodulation therapy

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Abstract

Objectives: Orthopedic implants have improved the quality of life in aging society but also induces several kinds of tissue reactions, referred to as orthopedic implant hypersensitivity (OIH). The aim of our study is to report the clinical characteristics of OIH and the effects of photobiomodulation therapy (PBMT) on these groups of patients. **Materials and Methods:** We collected cases that complained of skin rashes with pruritus after orthopedic implants from January 2017 to June 2022 at the Dermatology clinic in Hualien Tzu Chi Hospital. We recorded the sites and material of orthopedic implants, skin lesions onset time, symptoms, location after implantation, and the disease duration. Laboratory tests were measured, including complete blood count, differential count, serum immunoglobulin E (IgE) level, as well as inflammatory and autoimmune markers. PBMT, including UVB311 nm or low-level laser therapy 808 nm, was performed. Dose, duration, and response were documented. **Results:** Fourteen patients were diagnosed with OIH; twelve presented with localized eczema at the implant sites, and two with generalized eczema. Eleven patients (78.6%) had either elevated eosinophils percentage (>6%) or IgE level (>200 U/mL) or both. Seven patients (50%) had favorable outcome after PBMT and successfully withdrew from systemic steroid. **Conclusion:** In our case series, localized eczema at implant sites was a common cutaneous presentation in OIH. Hence, a surgical scar at the eczema site or long-term waxing and waning generalized eczema should prompt physicians on the possibility of OIH. Blood eosinophils percentage and serum IgE level can be reference biomarkers for OIH. PBMT provides a noninvasive and effective treatment strategy for immune regulation and tissue regeneration.

Keywords: *Aged, Eczema, Hypersensitivity, Orthopedic implant, Photobiomodulation therapy*

Introduction

With advancements in medical techniques, several kinds of implant devices are available for patients. Orthopedic implants such as artificial joints or metal screws/plates, dental implants, and cardiac implants are all commonly seen in clinical practices. A 15-year retrospective study of total knee replacement (TKR) therapy showed an increased incidence from 26.4 to 74.55 TKR per 100,000 inhabitants from 1996 to 2010 in Taiwan [1]. Despite the benefits of these implant devices, there are still some inevitable disadvantages, such as implant hypersensitivity reaction. The earliest case of orthopedic implant hypersensitivity (OIH) was reported in 1966, describing a case with localized eczema at the implantation site after metallic plate fixation [2]. Chang *et al.* demonstrated that eczema is the most common presentation of OIH; using the Taiwan National Health Insurance Research Database revealed that joint replacement patients had a 1.38- and 1.35-fold eczema risk in crude and multivariable Cox model. In addition, the cumulative incidence of eczema was approximately 6.21% higher in the joint replacement group compared with the control group after 14 years of follow-up [3]. With increasing case reports and attention to this topic, the prevalence of OIH has been studied and reported to be around 10%–17% in the general population [4]. In our experience, OIH is not a rare clinical scenario in dermatology clinics. However, without clear history taking

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and proper physical examinations, the diagnosis may be neglected easily. In our case series, we have detailed the onset, duration, treatment strategy, clinical follow-up, and responses in 14 patients with metallic OIH. Treatment for OIH is quite challenging due to most of the orthopedic implants are not removable or are permanent for functionality. Here, we present the experience of photobiomodulation therapy (PBMT) on the relief of OIH.

Materials and Methods

This case series study was approved by the Research Ethics Committee of Buddhist Tzu Chi General Hospital (Institutional Review Board 111-228-B).

Patients

We collected cases who complained of localized or generalized eczema with pruritus after orthopedic implants from January 2017 to June 2022 in the Dermatology Outpatient Department in Hualien Tzu Chi Hospital. The exclusion criteria of our case series are as follows: (1) Exact contact or medication exposure before the development of the skin lesions. (2) Skin biopsy proved lesions to be another definite skin inflammatory dermatoses.

Clinical history

Thorough history taking was performed, including the time and sites of orthopedic implants, the onset time, symptoms, and location of skin lesions after implantation, as well as the disease duration. The onset time was defined as the time between metal orthopedic implantation to the skin rash occurrence; disease duration was defined as the time from the skin rash appearance to the first visit to our outpatient department.

Serum markers

Laboratory tests, including complete blood count, differential count, serum immunoglobulin E (IgE) levels, and common inflammatory and autoimmune markers, including CRP, ESR, ANA, C3, and C4, were measured for each patient. An elevated eosinophil percentage is defined as >6% serum blood eosinophils. An elevated IgE level is defined as >200 U/mL.

Implant devices

X-rays of implantation sites were performed for the patients. The components of the implant materials were recorded based on the medical records and the brands of the patients' implants. The second confirmation of the implant materials was checked by the orthopedic surgeon, Dr. Tzai-Chiu Yu.

Photobiomodulation therapy

UVB 311 nm phototherapy was performed with Neolux® (Daavlin, Bryan, Ohio) as the light source. The initiation dose was 300 mJ/cm^2 with an escalation of 50 mJ/cm^2 every treatment. Low-level laser therapy (LLLT) 808 nm was performed with TI-816-8® (TRANSVERSE, New Taipei City, Taiwan). The total output power was 1800 mW. The treatment duration was 15 min per treatment with a total energy of 20.25 J per treatment area. The standard treatment frequency for UVB 311 nm and LLLT 808 nm was three times a week.

Results

Fourteen patients were diagnosed with OIH during the 5-year study period. The patient demographics and orthopedic implant details are presented in Table 1.

Patient demographics

The included patients were between 13 to 86 years old, with mean age and the median age of 62.4 and 68 years old, respectively, indicating OIH is more prevalence in the elderly group. There are a total of 18 implants in 14 patients, seven patients had hip, knee, or shoulder joint replacement, and the other seven had static implants such as plates or screws.

Table 1: Patient's demographics and clinical informations

Age	Sex	Implant site	Implant content	Onset time	Duration	Skin rash pattern		Eos counts 10^3/uL (%)*	IgE (U/mL)	Photobiomodulation therapy (cumulation dose)	
						Generalized	Localized			UVB 311 (J/cm^2)	LLLT 808 (J/Tx area)
81	Female	Bilateral TKR	Co-Cr-Mo	3 years	1 week		v	382 (6.1)	417		81
72	Female	Bilateral THR	Co-Cr-Mo; Ti-6Al-4V	>3 years	1 month		v	161 (2.7)	1580	1.5	
86	Female	Right TKR	Co-Cr-Mo	9 months	6 months		v	259 (3.6)	13.5	30.3	
61	Female	Right TKR	Co-Cr-Mo	3 years	2 years		v	517 (8.1)	105		
70	Male	Right shoulder replacement	Ti, Co-Cr	2 years	3 years		v	88 (1.4)	1720->697		344.25
77	Male	Bilateral THR	Co-Cr-Mo	>3 years	>10 years	v		166 (2.1)	842	0.75	
66	Male	Bilateral TKR	Co-Cr-Mo	>3 years	1 year	v		536 (6.9)	317		
74	Male	Left tibia	Ti-6Al-4V	3 months	2 months		v	332 (6.4)	77.3		
77	Female	Right tibia	Ti-6Al-4V	1 month	4 months		v	157 (2.5)	72.9		911.25
13	Male	Left tibia	Stainless steel	1 months	3 months		v	833 (6.3)	229	6.05	
23	Female	Right clavicle	Ti, Co-Cr	2 months	5 days		v	399 (6.4)	131		
63	Male	Spine	Ti, Co-Cr	>3 years	6 months		v	43 (0.5)	1428		
47	Female	Lumbar-spine	Ti, Co-Cr	1 year	1 year		v	208 (2.8)	1659		
64	Male	Lumbar-spine	Ti, Co-Cr	2 years	1 year		v	21 (2)	58.4		

TKR: Total knee replacement, THR: Total hip replacement, Tx: Treatment, LLLT: Low-level laser therapy, IgE: Immunoglobulin E

The onset time from implant placement to skin complaint ranged from 1 month to more than 3 years.

Most patients presented with localized eczema at the implant sites [Figures 1-3], and two patients presented with generalized eczema [Figure 4].

Implant materials

Six patients had cobalt (Co)-chromium (Cr) alloy implants. Two patients had Titanium (Ti) alloy implants. Six patients had both Co-Cr alloy and Ti alloy in their implants. One patient had stainless steel implant.

Laboratory results

Based on suspicion of OIH in these patients, we performed blood tests, including complete blood count, differential count, IgE level, and inflammatory and autoimmune markers during their outpatient visit. Three patients (21.4%) had both elevated eosinophils percentage (>6%) and IgE level (>200 U/mL), three (21.4%) had only elevated eosinophils percentage, five (35.7%) had only elevated IgE level, and three (21.4%) had normal eosinophil percentage and IgE level. In summary, 11 patients (78.6%) had either elevated eosinophils percentage (>6%) or IgE level (>200 U/mL) or both. There are no significant abnormalities in common inflammatory and autoimmune markers, including CRP, ESR, ANA, C3, and C4.

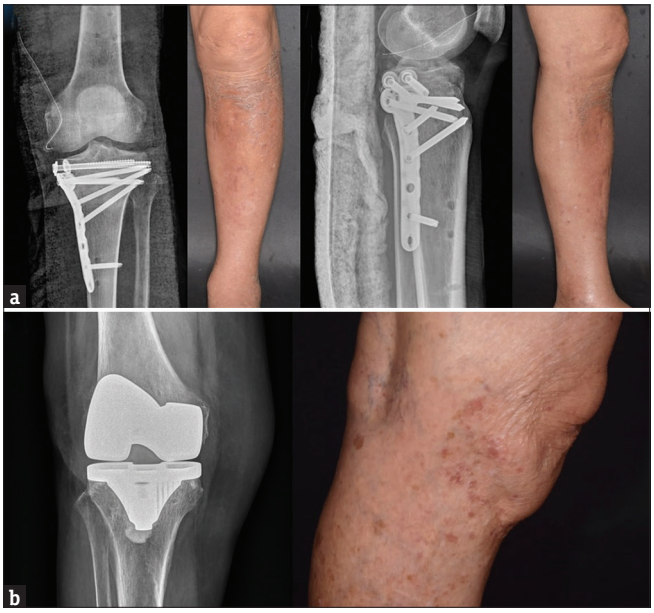

Figure 1: Implantation site X-ray and localized eczema. (a) Left tibia implantation X-ray and chronic eczema at left lower leg of Case 8. (b) Right total knee replacement X-ray and localized eczema at right knee of Case 3

Treatment strategies and responses

Several treatment modalities were adopted for these patients. The topical steroid with or without oral antihistamine was prescribed as the first-line therapy for all patients. Two patients had a complete response after 1 month of the first line of treatment. PBMT was considered for patients with inadequate response to topical steroids and oral antihistamines. Four patients underwent UVB 311 nm phototherapy, and 2 patients reported complete resolution after 1- and 4-month therapy, respectively. Figure 2 shows the favorable outcome of UVB 311 nm phototherapy with a cumulative dose of 6.05 J/cm^2 in a 13-year-old boy presenting localized OIH (Case No. 10). Three patients underwent LLLT 808 nm; two patients reported complete resolution after a 3-month therapy. Figure 3 shows how well a 77-year-old woman responded to LLLT 808 nm phototherapy after 3 months of treatment (Case No. 9). Erythema, swelling, and pruritus all subsided with residual postinflammatory hyperpigmentation. The major limitation of PBMT is the inconvenience to some patients for visiting the hospital three times per week, which lead to the disruption or discontinuation of the therapy. Three patients with partial response to PBMT are all owing to the interrupted treatment schedule.

Discussion

Eczema is the most common and earliest presentation of OIH. In our case series, localized eczema was the most common (85.7%) clinical manifestation of OIH. However, some patients may further develop generalized skin lesions (14.3%). The onset time from implant placement to cutaneous eruptions is variable among individuals from months to years after implantation. As of serum biomarkers of OIH, we found 40% with eosinophilia and 57% with elevated IgE levels. Either

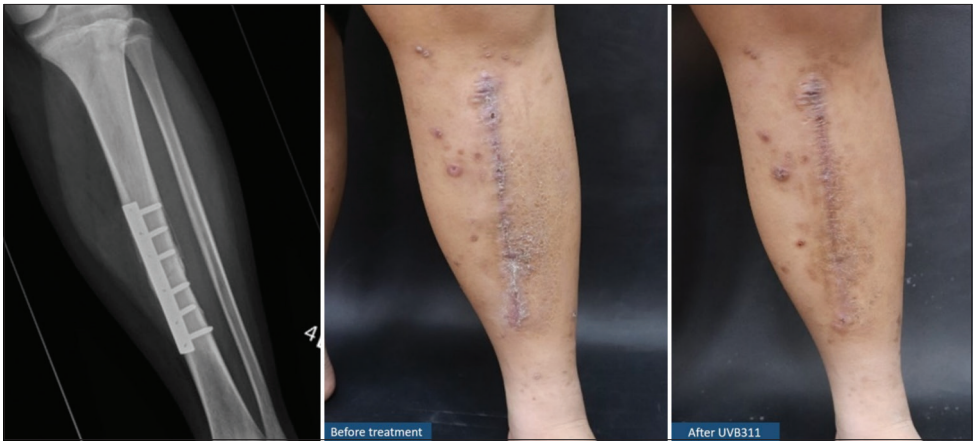

Figure 2: Case 10: Left tibia implantation X-ray, localized eczema at left shin (left and middle column). Improvement of left shin skin lesions after accumulated 6.05 J/cm^2 of UVB-311 nm phototherapy (right column)

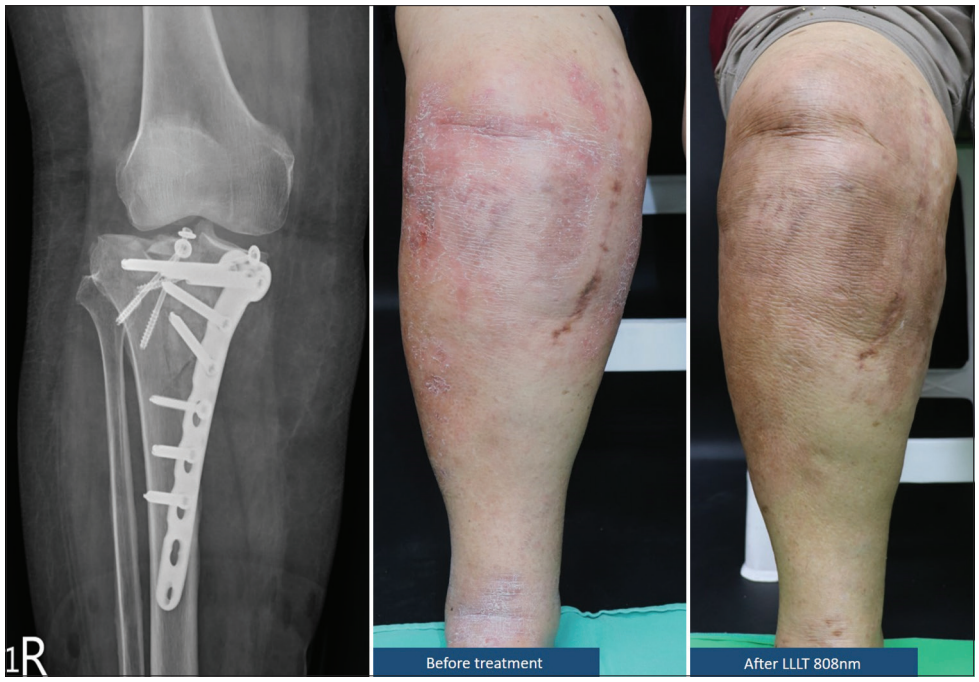

Figure 3: Case 9: Right tibia implantation X-ray, localized eczema at the right knee to shin (left and middle column). Improvement of the right knee and shin skin lesions after accumulated 911.25 J/treatment area of LLLT 808 nm phototherapy (right column)

Figure 4: Bilateral total hip replacement X-ray and generalized eczema of Case 6

elevated eosinophil percentage or IgE level is 78.4%, indicating blood eosinophils and IgE level are effective biomarkers for OIH. Another interesting and important finding is that of patients' age. The mean age of our patients is 62.4 years old, indicating OIH should be considered one of the most important etiologies of eczema among elderly people.

Several hypotheses have been proposed for the pathogenesis of OIH. Delayed-type (type IV) hypersensitivity is still viewed as the major response of OIH. However, unlike traditional allergic contact dermatitis, the sensitization phase of OIH occurs in different microenvironments other than the skin. The release of metal ions and wear particles into the soft tissue or joint space may activate both innate and acquired immune responses [5]. This may also explain the reasons for delayed onset (>3 years) of OIH while the metal implant gradually wears over time with subsequent and persistent releasing metal ions. A study of the cytokine profile in patients with aseptic loosening of total hip replacement revealed a significant increase in interleukin-1 (IL-1), IL-2, IL-4, IL-6, IL-8, granulocyte/macrophage colony-stimulating factor, interferon-gamma, and tumor necrosis factor-alpha-alpha levels in a peri-implant tissue [6]. This finding supports the involvement of innate and acquired immune responses in the peri-implant immunologic reaction. Furthermore, the development of generalized eczema may perhaps be viewed as an id reaction to localized metal implants.

Metal components in orthopedic implants include Co, Cr, Ti, Al, V, molybdenum (Mo), zirconium (Zr), nickel (Ni), and

stainless steel [7]. In our study, six patients had Co-Cr-Mo alloy implantation; five patients had Co-Cr alloy alongside Ti; three patients had Ti-6Al-4V alloy implantation, and one had stainless steel implantation.

In a large series of metal allergens studies in 2011, a patch test with 42 metal preparations was performed on over 1000 patients. The result revealed that 57% of patients had a least one positive reaction [8]. The most common metals which elicited positive reactions were Ni, gold, Co, Cr, and silver. Although Ti was reported to cause minimal allergic reactions in the past, we still observed OIH in patients with Ti alloys in our study. In one most recent meta-analysis, the prevalence of Ti hypersensitivity is increasing with the increased use of Ti implants [9]. Since orthopedic implants share common metal elements, it is impractical to perform patch tests before choosing which brand to implant; however, the information of the implant should be recorded in the patient's medical record to tracing the long-term side effects.

The current consensus of the most effective modality for the treatment of OIH is the removal of the implants or replacement with nonallergenic alloy implants [10]. Static implants for internal fixation of bone fractures, such as plates or screws, could be removed after fracture healing. On the contrary, artificial joints are unlikely to be removed and also not cost-effective to be replaced with other alloys. As for spinal implants, whether appropriate or not removing the implants depends much on the function of the implants and should be evaluated individualized. Considering the above situations, conservative treatment with an oral antihistamine and oral or topical corticosteroid is commonly prescribed first. However, long-term use of systemic steroids should be avoided due to its multiple adverse effects, especially osteoporosis, in this group of patients. Thus, for patients who are steroid dependent and are not able to remove or replace the implants, PBMT with UVB 311 nm phototherapy or LLLT 808 nm was suggested. UVB 311 nm was applied for patients with relatively superficially affected rashes indicating prominent epidermal and dermal-epidermal junction immune reactions. LLLT 808 nm was chosen for those with more infiltrated skin rashes and mild swelling or erythema around the joint. These patients reported significant improvement in pruritus and their skin lesions resolved after phototherapy combined with topical steroids. UVB 311 nm has long been used in several inflammatory skin diseases. It may lower the production of pro-inflammatory cytokines such as IL-1α, IL-2, IL-5, and IL-6 [11]. In our study, from the responses of our patients, UVB 311 nm was well-tolerated and yielded good effects. Local LLLT 808 nm was less commonly used in OIH patients in the past. Since 808 nm wavelength can successfully penetrate deeply through the skin to the subcutis, we hypothesized that LLLT 808 nm might have some immune-modulating role over soft tissue surrounding the implant. Several studies on acute joint inflammation were performed in rats using LLLT 808 nm therapy [12,13]. They discovered that a total 50 mW LLLT 808 nm treatment could reduce cellular inflammation and decrease inflammatory mediators such as IL-1β and IL-6. From the above-mentioned mechanism, the rationality of LLLT 808 nm treatment could be established, especially in patients with localized OIH. As LLLT 808 nm modulated the microenvironments around the implantation sites, the inflammatory reactions decreased and thus improved the cutaneous conditions. In summary, the concept of PBMT is getting more popular in recent years. As a non-invasive treatment modality, PBMT regulates several biological processes such as remodeling and reducing tissue inflammation as well as regeneration [14].

In this case series, the mean age of all included patients is 62.4 years old. However, being more specific in the joint replacement group (cases 1–7), the mean age is even older (73.2 years old). Therefore, we suggest that OIH is also one of the important geriatric issues. Developing effective but low-risk treatment modalities for these groups of patients is of great significance.

Conclusion

OIH are not uncommon in dermatologic clinics. Patients often present with either localized or generalized pruritic eczema with variable durations. A surgical scar at the site of eczema should prompt the physicians to consider local metal implantations. For patients with long-term waxing and waning generalized eczema, a detailed history of orthopedic implants should be obtained. As with other allergic reactions, OIH may also be associated with elevated IgE levels and eosinophil percentages. In clinical settings, implant removal may not be suitable for all patients with OIH. Some patients may have complete responses to topical and oral antihistamines, while others developed more severe diseases with systemic steroid dependence. Based on our findings, PBMT is an alternative treatment to avoid steroid complications. UVB-311 nm phototherapy is effective for patients with generalized eczema or skin eruptions with prominent epidermal changes. LLLT 808 nm is effective for those with more infiltrated skin eruptions with localized joint swelling and erythema. We first demonstrate PBMT as an effective treatment for OIH, possibly via the mechanisms of immune regulation and tissue regeneration.

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Nil.

Conflicts of interest

Dr. Chung-Hsing Chang, an editorial board member at *Tzu Chi Medical Journal*, had no role in the peer review process of or decision to publish this article. The other author declared no conflicts of interest in writing this paper.

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