

Management of Diabetic Foot Ulcer by Homoeopathy- A Case Report

Partha Pratim Pal¹, Satarupa Sadhukhan^{2*}, Sudeshna Saha²

¹Research Officer (H)/ S-1, ²Senior Research Fellow (H), Dr Anjali Chatterji Regional Research Institute (H), Kolkata, India

Abstract:

Diabetes mellitus (DM) is one of the major health issues. Patients with DM are prone to multiple complications including diabetic foot ulcer (DFU). DM increases the incidence of foot ulcers by 11-fold, which counts for more than 80% of all amputations. Reductions in frequency of the development of ulcer can be achieved by taking a multidisciplinary approach to patient management. Studies reveal promising effects of homoeopathy in reducing the associated symptoms and healing the ulcer. The given case is of a diabetic patient having a deep punched out foot ulcer. He was diabetic for the last 10 years and was under conventional anti-diabetic oral medication. The ulcer was above the medial malleolus in the left leg for 7 days. It was painless with burning and itching sensation near the margin with a yellowish pustular sticky discharge. The ulcer was of size 30 mm x 30 mm, depth of 3 mm, circular in shape, well-defined margin, with slough, yellowish floor. There was no extension or involvement to bones or tendon. As per Wagner system, it is found to be of grade-I. On the basis of totality of symptoms the case was analysed. Repertorization was done using Kent's repertory with the help of HOMPETH software. Subsequently, *Kali bichromicum* was the remedy of choice. Four doses of 200th centesimal potency, to be taken once daily, were prescribed. Assessment of the ulcer was done using Wagner system and photography of the lesion at the same angle with similar light exposure. By the end of one and half months, the ulcer was found to be healed up. Additionally, it was found that the blood glucose level also dropped down despite there was no modification in the ongoing conventional treatment. Observational studies and randomized controlled trials with sound methodology are recommended as next levels of evidence-based approach.

Keywords: Diabetes mellitus, Diabetic Ulcer, Case study, Homoeopathy, Kali bichromicum

Received: 11.10.2021 Revised: 15.11.2021 Accepted: 12.12.2021 Published: 25.12.2021

Quick Response code



*Corresponding Author:

Dr. Satarupa Sadhukhan,
Senior Research Fellow (H),
Dr Anjali Chatterji Regional Research Institute (H),
Kolkata, India
E-mail : satarupadsadhukhan@hotmail.com

Introduction:

Diabetes mellitus (DM) is one of the major health issues and a global public health threat that has increased dramatically over the past two decades. Patients with DM are prone to

multiple complications and one such is diabetic foot ulcer (DFU). ^[1,2] Diabetes increases the incidence of foot ulcers by 11-fold, which counts for more than 80% of all amputations. At the same time, it increases hospital costs

more than 10-fold over the 5 years ^[3]. It is usually the result of poor glycaemic control, underlying neuropathy, peripheral vascular disease, or poor foot care ^[4]. DFUs begin with neuropathy and peripheral vascular disorders. In diabetes, feet are more susceptible to trauma and infections due to neuropathy and vascular disorders as compared to non-diabetic feet. Neuropathy is characterized by a sensation of heat, numbness, and a dry feeling ^[5, 6].

The burden of DFUs on hospital admissions and costs are alarming. Rates of recurrence of foot ulcers are very high, being greater than 50% after 3 years. The majority of these costs are related to the treatment of infected foot ulcers. Education initiatives and early prevention strategies are essential to prevent further increase in economic burden ^[7]. Although not all foot complications can be prevented, dramatic reductions in frequency can be achieved by taking a multidisciplinary approach to patient management ^[8].

In a comparative study ^[9] of 840 patients with a current or past history of DFU or diabetes-related lower-extremity amputation (LEA) were recruited and followed for 6 years. The study concluded that diabetic patients with diabetic foot complications have an excess mortality rate when compared with diabetic counterparts without foot complications and the general population. Another study ^[10] have shown that the median time for healing of a DFUs was long, around 6 months and with a high recurrence rate. Integrated care for the diabetic foot in one National Health Service (NHS) health service area ^[11] over 18 years was associated with a reduction in first presentations of diabetic foot ulceration but failed to reduce recurrent ulceration. The use of therapeutic footwear with a rigid rocker sole in patients with diabetes with polyneuropathy and the history of a DFU is helpful to reduce the risk of plantar ulcer recurrence ^[12].

A meta-analysis of 10 studies ^[13] have pointed out that gram-negative bacteria were the most common reason for DFUs. The presence of

diabetic retinopathy (DR) and albuminuria (Alb) significantly increases the risk of development of DFUs. ^[14] A 12-month prospective observational study for people with an infected DFU confirms the adverse prognostic effect of limb ischemia, longer ulcer duration and the presence of multiple ulcers. ^[15] One systematic review ^[16] has found that hyperbaric oxygen therapy (HBOT) significantly improved the ulcers healed in the short term but not the long term. No definitive conclusion was drawn by another study ^[17] done to find out the clinical and cost-effectiveness of standard wound care plus HBOT versus standard wound care alone for the treatment of DFUs. Stem cell therapy ^[18] is an effective treatment for DFUs and is currently used as an alternative to amputation for some patients without other options for revascularization. The administration of the *Ceratothoa oestroides* extract ointment proved to be effective in one case. ^[19] According to another case report of neuroischaemic DFU, ^[20] weekly dressings with collagen implant impregnated with gentamicin sulphate had a favourable outcome. There is a guideline containing 10 key recommendations to guide health professionals in selecting the most appropriate footwear to meet the specific foot risk needs of an individual with diabetes. ^[21]

In a retrospective cohort study, ^[22] individualized homeopathic treatment was associated with better glycaemic control when compared with standard conventional treatment alone. A prospective, observational study ^[23] of 156 patients with DFU with positive results has been published. It was conducted by the Central Council for Research in Homoeopathy at its Drug Standardization Extension Unit, Hyderabad, from October 2005 to September 2009; Homeopathic medicines prescribed to the enrolled patients were limited to a group of 15 pre-defined trial medicines. The improvement of the cases was assessed based upon the DFU assessment score, before and after treatment, on

a prescribed format devised by the council and by periodic photographs.

In a case series of gangrene, 5 cases are presented, in which the homoeopathic treatment prevented amputation of the concerned body part ^[24]. Four out of five were related to type II DM. Another case series ^[25] analyzing the role of Silicea in DFU has also been published. Few case reports of DFU are already published where homoeopathic treatment has shown promising results. ^[24,26,-27]

Case Report:

A male diabetic patient of 44 years, Mr. K. B., visited to the OPD on 05.01.2021 with an ulcer above the medial malleolus in the left leg. He was diabetic for the last 10 years and was under allopathic anti-diabetic medication. The ulcer was there for 7 days and had an appearance of a deep punched out lesion, with no pain but there was a burning and itching sensation near the margin of the ulcer with a yellowish pustular discharge. On enquiry, among the generalities the patient had a general tendency to take cold, perspiration was profuse and occurs all over the body and there is post-meal heaviness, felt in the epigastrium, especially after lunch. He was under conventional treatment, was taking Metformin 500 mg, twice daily, orally.

On examination - Size: 30mm x 30 mm, Shape: circular, Depth: 3 mm, Margin: well-defined, Floor: slough, yellowish in colour, Discharge: purulent sticky discharge, no extension or involvement to bones or tendon. As per Wagner system ^[28], which is for assessment of ulcer depth, it is found to be grade-I (Figure 1). His built was mesomorphic, with good nutritional status. Clinical assessment reveals other parameters within normal limit. His height was 172 cm, weight was 65 Kg. As per the biochemical test, plasma glucose fasting was 271 mg/dl and post-prandial blood glucose was 343 mg/dl (Figure-2).

The symptoms were evaluated and the case was analysed accordingly. The totality of symptoms was chalked out on the basis of general symptoms as well as particular symptoms. Miasmatic analysis ^[29] was done thereafter (Table1). The case was found to be a case with psoric predominant state. This was followed by repertorial analysis as per Kent's method ^[30] using HOMPAT software ^[31] (Figure -3).

Kali bichromicum 200 was prescribed, 4 doses, once daily on every morning for consecutive 4 days, on 05.01.2021. Each dose consisted of 4 globules of no. 30. The patient was also advised to maintain wound hygiene and to follow diabetic diet and regime. Subsequent follow-ups are mentioned in Table 2.

Table -1: Miasmatic analysis:

Rubric	Miasm
Skin, ulcers, deep (p. 1223)	Psora
Skin, ulcers, discharges, yellow (p. 1223)	Psora
Extremities, pain, burning, leg (p. 1011)	Psora
Stomach, heaviness, eating, after (p. 454)	Psora
Perspiration, profuse (p. 1201)	Psora, Latent Psora, Syphilis
Generalities, cold, tendency to take (p. 1231)	Psora, Latent Psora, Syphilis

Table- 2: Subsequent follow-ups:

Date	Indication of Prescription	Medicine
1 st Follow-up 19.01.2021	No sloughing is present in the ulcer. Ulcer almost healed up. Scab formation occurs. No discharge or offensive odour was there.	Placebo was prescribed for one month

	Wagner Grades: 0; Figure 4.	
2 nd Follow-up 18.02.2021	The ulcer is healed up completely. Wagner Grades: 0; Figure 5. Another blood test done on 05.02.21 shows plasma glucose fasting was 152 mg/dl and post-prandial was 239 mg/dl, Figure 6.	<i>Berberis Aquifolium</i> ointment was given for external application (OD)

Table- 3: Assessment according to MONARCH:

Item	Yes	No	Not sure or N/A
1. Was there an improvement in the main symptom or condition for which the Homoeopathic medicine was prescribed	+2		
2. Did the clinical improvement occur with a plausible time frame relative to the drug intake?	+1		
3. Was there an initial aggravation of symptoms?		0	
4. Did the effect encompass more than the main symptom or condition, (i.e. were other symptoms ultimately improved or changed)?	+1		
5. Did overall wellbeing improve?	+1		
6. (A). Direction of cure: did some symptoms improve in the opposite order of the development of symptoms of the disease?	+1		
6. (B). Direction of cure: did at least two of the following aspects apply to the order of improvements of symptoms: From organs of more importance to those of less importance From deeper to more superficial aspects of the individual From the top downwards			Not sure
7. Did 'old symptoms' (defined as non-essential and non-cyclical symptoms that were previously thought to have resolved) reappear temporarily during the course of improvement?		0	
8. Are there alternate causes (other than the medicine) that – with a high probability – could have caused the improvement? (consider known course of disease, other forms of treatment and other clinically relevant intervention)		+1	
9. Was the health improvement confirmed by any objective evidence? (e.g. lab test, clinical observation etc.)	+2		
10. Did repeat dosing, if conducted create similar improvement?			N/A



Figure 1: Ulcer in the baseline

BIO-TECH
AN ISO 5001 : 2008 CERTIFIED COMPANY

TEST REPORT
A Leading Pathological Laboratory

Patient Name : MR. K. B. Male / 44 Year
Ref. By : SELF
Sample Date : 04-Jan-2021 Report Date : 04-Jan-2021
ID No. : DPZ - 16327

BIOCHEMISTRY

INVESTIGATION	RESULT	UNIT	REFERENCE VALUE
Plasma Glucose (Fasting)	271.0	* mg/dl	[70 - 110]
Plasma Glucose (PP)	343.0	* mg/dl	< 145

* Checked Twice

Figure 2: Plasma glucose fasting and post-prandial at the baseline

Search Words: Query (Enter Only Main Keywords) Recorded Symptoms

Rep.Chapters: Q. Pinned X

Select Report: All

Repertoriations: Normal

Clipboard

Symptom Options Remedy Options Sym Methods

Remedy Name	10	12	11	10	10	10	9	9
[Kant] [Skin] [Ulcers/Discharges/Yellow]	5	5	5	5	4	4	4	4
[Kant] [Extremities pain/Burning/Leg]	2	3	2	1			1	
[Kant] [Skin] [Ulcers/Deep]	3	3	3	2	3	3	3	3
[Kant] [Stomach/Heartburn, weight oppression (see...)]	3	2	3	3	2	2		1
[Kant] [Pericardium/Protrude]	3	3	2	3	2	3	3	2

Symptoms Covered

[Kant] [Skin] [Ulcers/Discharges/Yellow]	5	5	5	5	4	4	4	4
[Kant] [Extremities pain/Burning/Leg]	2	3	2	1			1	
[Kant] [Skin] [Ulcers/Deep]	3	3	3	2	3	3	3	3
[Kant] [Stomach/Heartburn, weight oppression (see...)]	3	2	3	3	2	2		1
[Kant] [Pericardium/Protrude]	3	3	2	3	2	3	3	2

Figure 3: Repertorial analysis



Figure 4: Ulcer in first follow-up



Figure 5: Ulcer in second follow-up

Health
With You, Always

Name: Mr. K. B. Client Name: 24PGS(N)-V
Age/Gender: 46 Y/Male Client Address: ASHOKNAGAR
Lab No: 022102050410 Referred By: Dr. SELF ADVICE
Ref Hospital: BABUN 9738723466 @461

Barcode No: 2433939
Registered on: 05/Feb/2021
Receiving on: 05/Feb/2021
Reported on: 05/Feb/2021

Test Name	Result	Unit	Biological Ref.Interval	Method
*Fasting Blood Glucose (FBS)	152	mg/dL	70 - 110	Hexokinase
Sample Type: Fluoride Plasma				

Interpretation:
 *A fasting plasma glucose level below 100 mg/dL is considered normal.
 *A fasting plasma glucose level between 100-126 mg/dL is considered as glucose intolerant or pre-diabetic. A fasting and post-prandial blood sugar level (after consumption of 75 gm of glucose) is recommended for all such patients.
 *A fasting plasma glucose level of above 126 mg/dL is highly suggestive of a diabetic state. A second fasting test is strongly recommended for all such patients. A fasting plasma glucose level in excess of 126 mg/dL on both the occasions is confirmatory of a diabetic state.
 Blood Glucose is maintained by a complex interplay of hormones. In diabetes (both Type 1 & Type 2), various genetic, metabolic and environmental factors lead to progressive loss of beta cell mass or insulin sensitivity, manifesting as hyperglycemia. Several events (eg. infection, stress, surgery, trauma) can may worsen glycemic control. Any condition leading to deterioration of glycemic control requires more frequent monitoring of blood glucose.

Reference:
 CLASSIFICATION AND DIAGNOSIS OF DIABETES: STANDARD OF MEDICAL CARE IN DIABETES - 2018. Diabetes Care 2018.

*Postprandial Glucose (PP)	239	mg/dL	70 - 140	Hexokinase
Sample Type: Fluoride Plasma				

Interpretation:
 Blood Glucose is maintained by a complex interplay of hormones. In diabetes (both Type 1 & Type 2), various genetic, metabolic and environmental factors lead to progressive loss of beta cell mass or insulin sensitivity, manifesting as hyperglycemia. Several events (eg. infection, stress, surgery, trauma) can may worsen glycemic control. Any condition leading to deterioration of glycemic control requires more frequent monitoring of blood glucose.

Figure 6: Plasma glucose fasting and post-prandial after one month

Discussion:

The final causal attribution score, in this case, was assessed using the Modified Naranjo Criteria for Homoeopathy (MONARCH), as proposed by the HPUS Clinical data Working Group, June 2014 [32]. The total score was 9 after the end of one and half months of treatment, suggesting a 'definite' association between the medicine and the outcome (Table 3) [definite: ≥ 9 ; probable 5-8; possible 1-4; and doubtful ≤ 0]. Reporting of this case follows the Hom-CASE-CARE guidelines [33]. Presently, after 7 months of the last follow-up mentioned over here, the patient is having normal blood glucose level without any recurrence of ulcer. In the present case, we have assessed the causal attribution of homoeopathic medicine with the clinical presentation using MONARCH. Wagner system was used for assessment of the case before and after treatment apart from the blood biochemistry report. Photographs of the lesion clicked from the same angle with similar light exposure were also used. As photographic evidences are considered to be of low diagnostic accuracy, it may be taken as one of the two limitations of the case report. The second being lack of use of any Quality of life scale that could have been used as another outcome measure. A remarkable difference in plasma glucose level was obtained in one month and it was assessed as per the blood reports. Despite the patient was already on anti-diabetic medication (Metformin), the blood parameters were quite high when he came for the treatment of DFU. But along with the gradual healing of the ulcer, Grade 1 of Wagner system to Grade 0, the blood glucose levels also decreased considerably. Chemically, Kali bichromicum is irritating to skin and mucous membrane and hence it may cause external ulcers known as 'chrome sores' [34]. Therapeutically, it has variable symptoms related to skin and hence knowledge of toxicology once again, appropriately furnishes the first rudiments of materia medica in the antitype of Kali Bichromicum [35] also. In a

prospective observational study Homoeopathy as mentioned above, the homoeopathic drugs Silicea, Sulphur, Lycopodium, Arsenicum album and Phosphorus were found to be useful in the treatment of DFU [23]. Furthermore detailed study of case reports revealed that the drugs Silicea, Sulphur, Lachesis were mainly used along with Sepia and Medorrhinum were used to treat DFU. [24, 25, 27]

Conclusion:

Homoeopathic medicines may be useful in treating DFU. Observational trials and randomized controlled trials with sound methodology can be applied before making any firm recommendations.

Limitation of study:

This is single case study so it needs to be tried this intervention in a greater number of cases for its scientific validation.

Patients consent:

The consent of patient has been taken before treatment and also for the publication of images without disclosing the identity of patient.

References:

1. Shahbazian H, Yazdanpanah L, Latifi SM. Risk assessment of patients with diabetes for foot ulcers according to risk classification consensus of International Working Group on Diabetic Foot (IWGDF). *Pak J Med Sci.* 2013;29:730-734.
2. Pendsey SP. Understanding diabetic foot. *Int J Diabetes Dev Ctries.* 2010; 30:75-79.
3. Hicks CW, Selvarajah S, Mathioudakis N, et al. Burden of infected diabetic foot ulcers on hospital admissions and costs. *Ann Vasc Surg.* 2016; 33:149-158.
4. Oliver TI, Mutluoglu M. Diabetic foot ulcer. 2019. Available from: <https://europepmc.org/article/nbk/nbk537328> [last accessed on 26.09.2021]

5. Volmer-Thole M, Lobmann R. Neuropathy and diabetic foot syndrome. *Int J MolSci* 2016; 17:917.
6. Bajaj S. RSSDI clinical practice recommendations for the management of type 2 diabetes mellitus 2017. *Int J Diabetes Dev Ctries*. 2018;38:1-15.
7. Andrew J, Gunne R, Jan A. The global burden of diabetes foot disease. *Lancet*. 2005; 366:1719-1724.
8. Frykberg RG, Zgonis T, Armstrong DG, et al. Diabetic foot disorders: a clinical practice guideline (2006 revision). *J Foot Ankle Surg*. 2006; 45:S1-66.
9. Al-Rubeaan K, Almashouq MK, Youssef AM, et al. All-cause mortality among diabetic foot patients and related risk factors in Saudi Arabia. *PLoS One*. 2017;12:e0188097.
10. Sørensen ML, Jansen RB, Wilbek Fabricius T, Jørgensen B, Svendsen OL. Healing of Diabetic Foot Ulcers in Patients Treated at the Copenhagen Wound Healing Center in 1999/2000 and in 2011/2012. *Journal of Diabetes Research*. 2019; 36:1424-1430.
11. Paisey RB, Abbott A, Paisey CF, et al. Diabetic foot ulcer incidence and survival with improved diabetic foot services: an 18-year study. *Diabetic Medicine*. 2019;36:1424-1430.
12. López-Moral M, Lázaro-Martínez JL, García-Morales E, et al. Clinical efficacy of therapeutic footwear with a rigid rocker sole in the prevention of recurrence in patients with diabetes mellitus and diabetic polyneuropathy: A randomized clinical trial. *PloS one*. 2019;14:e0219537.
13. Zubair M. Prevalence and interrelationships of foot ulcer, risk-factors and antibiotic resistance in foot ulcers in diabetic populations: A systematic review and meta-analysis. *World J Diabetes*. 2020;11:78.
14. Tomita M, Kabeya Y, Okisugi M, et al. Diabetic microangiopathy is an independent predictor of incident diabetic foot ulcer. *Journal of Diabetes Research*. 2016. DOI:10.1155/2016/5938540.
15. Ndosi M, Wright-Hughes A, Brown S, et al. Complications Prognosis of the infected diabetic foot ulcer: a 12-month prospective observational study. *Diabetic Medicine*. 2018;35:78-88.
16. Kranke P, Bennett MH, Martyn-St James M, et al. Hyperbaric oxygen therapy for chronic wounds. *Cochrane Database Syst Rev*. 2015;2015:CD004123.
17. Health Quality Ontario. Hyperbaric oxygen therapy for the treatment of diabetic foot ulcers: a health technology assessment. *Ontario Health Technology Assessment Series*. 2017;17:1.
18. Lopes L, Setia O, Aurshina A, et al. Stem cell therapy for diabetic foot ulcers: a review of preclinical and clinical research. *Stem Cell Res Ther*. 2018;9:188.
19. Meimeti E, Tentolouris N, Loupa C, et al. Marine isopod *Ceratothoa oestroides* extract: A novel treatment for diabetic foot ulcers? Case report of an immunosuppressed patient. *Medical Archives*. 2019;73:131.
20. Almeida CC. Collagen implant with gentamicin sulphate as an option to treat a neuroischaemic diabetic foot ulcer: Case report. *Internat J Surg Case Report*. 2016; 21:48-51.
21. Van Netten JJ, Lazzarini PA, Armstrong DG, et al. Diabetic Foot Australia guideline on footwear for people with diabetes. *J Foot Ankle Res*. 2018;11:1-4.
22. To KL, Fok YY, Chong KC, et al. Individualized homeopathic treatment in addition to conventional treatment in type II diabetic patients in Hong Kong—a retrospective cohort study. *Homeopathy*. 2017;106:79-86.
23. Nayak C, Singh V, Singh K, et al. A Prospective Observational Study to

- Ascertain the Role of Homeopathic Therapy in the Management of Diabetic Foot Ulcer. *AmJ Med.* 2011;104:166-176.
24. Mahesh S, Mallappa M, Vithoulkas G. Gangrene: Five case studies of gangrene, preventing amputation through Homoeopathic therapy. *Indian J Res Homoeopathy* 2015;9:114-122.
25. Ponnam HB, Gupta J. Role of Silicea in Diabetic Foot Ulcer: A Retrospectively Analyzed Case Series. *Homoeopathic Links.* 2020;33:53-58.
26. Murthy K, Murthy DA. A Case Report on Diabetic Foot Gangrene. *Homoeopathic Links.* 2017;30:259-261.
27. Ali MS, Bindu HP. A case of Diabetic Foot Ulcer: Homoeopathic Treatment could avoid Amputation. *The Homoeopathic Heritage.* 2009;34:35-38
28. Oyibo SO, Jude EB, Tarawneh I, et al. A comparison of two diabetic foot ulcer classification systems: the Wagner and the University of Texas wound classification systems. *Diabetes Care.* 2001;24:84-88.
29. Patel RP. Chronic miasms in homoeopathy and their cure with classification of their rubrics/symptoms in Dr. Kent's repertory. Indian ed. Indian Books and Periodicals Publishers. New Delhi. 1996:454, 1011, 1201, 1223, 1231
30. Patel R. The Art of case taking and practical repertorisation in Homoeopathy. 6th edition. Sai Hahnemann Book Corporation Hahnemann House. Kerala. 1998: 77
31. Shah J. Homopath Classic-Homeopathic Software. Version 8.0 Premium. Mumbai; 2005
32. Rutten L. Data collection: Treat every variable as a treasure. *Homeopathy.* 2015; 104:190-196.
33. Van Haselen RA. Development of a supplement (HOM-CASE) to the CARE clinical case reporting guideline. *Complement Ther Med.* 2016; 25:78-85
34. Potassium dichromate. Available from <https://pubchem.ncbi.nlm.nih.gov/compound/Potassium-dichromate> (last cited on 10.11.2021)
35. Hahnemann S. *Organon of Medicine.* 26th impression, translated from the fifth edition with an appendix by R. E. Dudgeon, with additions and alterations as per sixth edition, translated by William Boericke and introduction by James Krauss. New Delhi: B. Jain Publishers (P) Ltd.; 2010.

Guarantor: Corresponding author is guarantor of this article and its contents.

Conflict of interest: Author declares that there is no conflict of interest.

Source of support: None

Financial Support and Sponsorship:

This patient came to the Out-Door Patient Department of Dr. Anjali Chatterjee Regional Research Institute (DACRRI). Medicines were procured from DACRRI dispensary. Expenses of laboratory investigations were done by the patient party.

How to cite this article:

Pal PP, Sadhukhan S, Saha S. Management of Diabetic Foot Ulcer by Homoeopathy- A Case Report. *Int. J. AYUSH CaRe.* 2021; 5(4):290-297.