

## Disulfiram and low nickel diet in the management of hand eczema: A clinical study

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### ABSTRACT

**Background:** Hand eczema due to nickel sensitivity is a challenging task for the dermatologist. The average human diet provides sufficient amount of nickel, which acts as a provoking factor in nickel-sensitive individuals. When such patients are treated with steroid or other immunosuppressives, only short-term remission is obtained. This is because unless the dietary intake of nickel is minimized and the existing amount of nickel in the body of the sensitized individual is depleted, long-term remission is unlikely. **Aim:** To evaluate the efficacy of oral disulfiram, a nickel-chelating agent and low nickel diet (LND) in reducing the clinical symptoms and preventing frequent relapse of hand eczema in nickel-sensitive individuals. **Methods:** A total of 21 patients with chronic vesicular hand eczema with nickel sensitivity were taken for this study. Patients were randomly divided into two groups: (a) Study group consisting of 11 patients (8 females and 3 males). They were prescribed disulfiram orally for a period of 4 weeks; they started LND 2 weeks prior to initiation of disulfiram therapy and continued till the end of follow-up period. (b) Control (placebo) group consisting of 10 patients (7 females and 3 males). They were allowed to continue with normal diet. Each of them received lactose tablet daily as placebo for 4 weeks. It was a comparative study and participants were not aware if they belonged to study group or control group (single blind trial). **Results:** Hand eczema healed completely in 10 (90.9%) out of 11 patients treated with disulfiram and LND during the treatment period in the study group, compared with 1 out of 10 patients in control (placebo) group (non significant). Mild relapse was noted in 5 patients in between 2-12 weeks of follow-up period. **Conclusion:** Low nickel diet and short course of oral disulfiram therapy can be considered a good option for the control of chronic hand eczema in nickel-sensitive individuals.

**Key Words:** Disulfiram, Hand eczema, Nickel

Hand eczema is a common and distressing dermatological condition. It is a chronic and recurring problem. The exact prevalence rate of hand eczema in India is not known. However, in the West, the prevalence rate is found to be 8%<sup>[1]</sup> among the adults in the general population and the 1-year prevalence is up to 10%<sup>[2]</sup> in the age group of 16-19 years. Hand eczema is caused by various exogenous and endogenous factors; one of the exogenous factors is

ingested nickel. It has been observed that ingested nickel can provoke or aggravate hand eczema in a sensitized individual and such sensitive individual develops flare of existing hand eczema after taking nickel orally.<sup>[3]</sup>

Nickel sensitivity is common in the general population and the prevalence rate varies from 4 to 13.1%.<sup>[4,5]</sup> It has been noted that nickel sensitivity is more common

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among females and the prevalence rate is about 10%.<sup>[6]</sup>

The incidence of hand eczema in nickel-sensitive individuals varies from place to place. According to a Danish study, the incidence rate was found to be 40%.<sup>[7]</sup> In an Indian study, the incidence rate was found to be 18%.<sup>[8]</sup>

The commonest clinical presentation of hand eczema induced by ingested nickel is 'dyshidrotic,' vesicular eczema.<sup>[3]</sup> Such type of eczema tends to run a chronic relapsing course. Different types of treatment have been recommended - wet dressing, topical steroid, systemic steroid, cyclosporin and other immunosuppressives, PUVA, etc. The result of treatment of such hand eczema is mostly unsatisfactory as the relapse rate is high. This is because nickel is present in most of the dietary items of human beings and an average diet supplies 300-600  $\mu\text{g}$ <sup>[9]</sup> of nickel to the human body; unless this continuous supply of nickel is curtailed or at least reduced, such type of hand eczema will continue to relapse.

So far, several studies have been made on low nickel diet<sup>[10]</sup> and nickel-chelating agents like disulfiram.<sup>[11]</sup> Some of these studies<sup>[12,13]</sup> have confirmed the benefit of low nickel diet and disulfiram.

The present study was designed to evaluate the efficacy of oral disulfiram and LND in reducing the clinical symptoms and preventing frequent relapse in such cases. It was a comparative hospital based study where oral disulfiram was given for a period of 4 weeks to 11 nickel-sensitive patients who were suffering from chronic, recurring hand eczema and were under LND. The result was compared with 10 nickel-sensitive patients who were suffering from chronic, recurring hand eczema and were on normal diet receiving placebo.

## METHODS

A total of 95 cases with chronic, recurring, vesicular type of hand eczema were taken for this study. A thorough clinical history and examination was taken for each patient. Patients with atopic diathesis, those with history to exposure to contact irritants or those

in whom a clinical suspicion of id eruption as well as septic focus cannot be ruled out; Those using prosthesis, e.g., orthodontic appliance, intramedullar nail, etc; pregnant and lactating mothers; those with a history of alcoholism; and those with abnormal biochemistry (sugars and liver function tests) or blood counts were excluded from the study.

Those selected were subjected to patch tests using Indian Standard Battery of Allergens approved by Contact Dermatitis Forum of India (CODFI). Of these, 21 patients (15 female and 6 male) who were found allergic to nickel alone were finally selected for this study. A valid written consent was obtained from each patient.

All the 21 patients were allowed to take nickel orally. Each of the patients was given 1 mg of nickel sulfate, which is approximately two times higher than the average dietary nickel. When examined after 24 h, only 4 patients responded with increased itching and 3 of them had new vesicular lesions.

The remaining 17 patients were then allowed to take 3 mg of nickel sulfate orally. Of these, 14 patients responded with increased itching and 8 of them had increased vesiculation. For the remaining 3 patients, no further trial with higher doses of nickel sulfate was done, as safe higher limit of oral nickel sulfate for provocation test is not proved till date. Moreover, there were reports of serious reactions like erythema multiforme<sup>[14]</sup> and vasculitis<sup>[15]</sup> following oral challenge.

All the 21 patients were randomly divided in two groups. *Study group (11 patients):* These patients were given a list of dietary items that contain higher amount of nickel. They were instructed to avoid these items in their food till the end of follow-up. Considering the food habit of the local community and convenience of the participants, each participant was given a list of foods that could be consumed during treatment and follow-up period. Such low nickel foods included milk, flattened rice, rice, paneer, fish, meat and eggs. Foods with partial restriction included green gram (*mung daal*), potato and, if the patient insisted, green leafy vegetables.

For cooking, mustard oil was allowed. Participants were also allowed to use butter and *ghee*, if they wanted. Sugar, salt, chillies were allowed. *Garam masala* was allowed to cook meat, fish and eggs. Patients were reviewed at intervals of 2 weeks. Apart from the clinical examination, a thorough diet history was taken from each participant on each visit. All the information received from the patients was noted in a diary. The need to stick to the diet prescribed (LND) was emphasized during each visit.

After starting with LND for 2 weeks, each of the patients was then given disulfiram 125 mg/day orally. The dose was increased to 250 mg/day from the second week to the fourth week of treatment. After completion of 4 weeks, each patient was followed up at 2-week intervals for a period of 12 weeks. During the 12-week post-treatment follow-up, all the patients in the study group were advised to continue with the LND. Blood counts, blood sugar and liver function tests were estimated at baseline, at the end of 4 weeks of disulfiram therapy, and at the end of follow-up.

*Control group (10 patients):* These patients were allowed to continue with normal diet. Each of the patients was given a placebo tablet (lactose tablet), orally, daily for a period of 4 weeks. Blood counts, blood sugar and liver function tests were estimated again at the end of 4 weeks. Patients with infected hand eczema in either group were first treated with oral and topical antibiotics prior to the initiation of therapy.

Patients of either group were allowed to apply petroleum jelly topically during the treatment period. The patients of the study group were advised to continue with the same topical application during the follow-up period. No patient was allowed to use steroid (both topical and oral) and other immunosuppressives during this period.

The severity of hand eczema was measured by using various parameters as in Table 1. Each patient was assessed at 2-week intervals; severity score was calculated and documented.

**Table 1: Severity parameters and grading scores for hand eczema**

Parameter	Severity	Score	
		Single palm	Both palms
Itching	Absent	0	0
	Mild	1	2
	Moderate	2	4
	Severe	3	6
Vesicles	Absent	0	0
	Involve < S1/3 palm	1	2
	Involve < T2/3 palm	2	4
	Entire palm	3	6
Crusting	Absent	0	0
	Present	1	2
Scaling	Absent	0	0
	Mild	1	2
	Moderate	2	4
	Severe	3	6
Fissuring	Absent	0	0
	Present	1	2

## RESULTS

### Study group

Ten (90.9%) out of 11 patients in the study group had complete clearance of their hand eczema at the end of 4 weeks' treatment with disulfiram [Table 2]. Only 1 patient continued to suffer from recurrence; but her clinical symptoms were reduced to minimum.

A drastic reduction in the recurrence rate was noted among the patients. Three out of 11 patients had very frequent attacks of hand eczema (1-2 attacks/month). Complete clearance of hand eczema was noted in two of them. The third patient showed improvement of hand eczema; she had mild itching but no vesicular lesion on the hand.

Other five patients who had been experiencing attacks of hand eczema at least once a month had complete clearance of skin lesion at the end of 4 weeks of disulfiram therapy. The remaining three patients who had attack of hand eczema at least once in 2 months had complete clearance of hand eczema.

The medicine was well tolerated by 6 patients (54.5%). Side effects of disulfiram were few and milder in nature; they were metallic taste (3 patients), mild drowsiness (2 patients) and anorexia. Of the 11 patients, only 3 (27.3%) showed mild elevation of liver enzymes.

**Table 2: Result of 4 weeks disulfiram therapy with low-nickel diet (study group)**

Sr. No.	Sex	Age	Duration (years)	Recurrence (years)	Total severity score (weeks)		
					0	2	4
1.	F	20	2	1-2 times / month	10	4	0
2.	F	25	3	1-2 times / month	18	6	0
3.	F	27	5	At least once a month	14	2	0
4.	F	35	2	At least once in 2 months	10	2	0
5.	F	39	2.5	At least once a month	10	2	0
6.	F	42	4	1-2 times / month	16	8	4
7.	F	45	2	At least once in 2 months	10	2	0
8.	F	50	5	At least once a month	16	8	0
9.	M	18	1	At least once a month	8	0	0
10.	M	22	2	At least once in 2 months	10	4	0
11.	M	31	3.5	At least once / month	14	6	0

F= Female; M=Male

\*Parameters which were evaluated for calculating the total severity score included itching, vesiculation, oozing, crusting, fissuring, scaling

**Control group**

Only 1 (10%) out of 10 patients showed signs of improvement [Table 3]. He had no itching, no scaling and no more vesicular eruption at the end of 4 weeks of placebo therapy. The remaining 9 patients continued to have recurrences of hand eczema with itching and vesicular lesions. Crusting was seen in 3 out of 9 patients, whereas scaling was observed in 2 out of 9 cases. No side effect of the medicine (e.g., placebo) was experienced by any of the patients.

Statistical analysis showed that improvement in severity score in the study group in comparison to the control group was statistically significant ( $P < 0.001$  unpaired t test).

Post-treatment follow-up of the study group at 2-week intervals for a period of 12 weeks [Table 4] showed that only 2 patients required a repeat one-week course of disulfiram while two others required symptomatic therapy with antihistamines and reinforcement of

dietary advice. The rest of the patients were free of significant symptoms or signs. Routine blood parameters and liver enzyme levels were examined again at the end of 12 weeks; no significant changes were noted in any of these 11 patients.

**DISCUSSION**

Nickel constitutes about 0.008% of the earth's crust and the soil contains 40 ppm of nickel on an average. It is present in most of the dietary items. Major dietary source of nickel is plant food. Plant tissue contains about four times more nickel than animal tissue. Therefore, total dietary intake of nickel per day varies depending on the amount of plant and animal food consumed. Dietary intake of nickel is about 300-600 µg/day on an average. Only 1-10% of dietary nickel is absorbed from the gut. Indian diet is rich in plant food in comparison to Western food, which is rich in animal food. Cow's milk, which is an essential part of majority of Indian diet, is not free from nickel and its

**Table 3: Result of 4 weeks of placebo therapy (control group)**

Sr. No.	Sex	Age	Duration (years)	Recurrence (years)	Total severity score (weeks)		
					0	2	4
1.	F	24	1	At least once a month	10	8	14
2.	F	29.5	2.5	At least once a month	10	12	14
3.	F	40	2	At least once a month	12	8	14
4.	F	42	5	1-2 times / month	14	16	16
5.	F	44	4	1-2 times / month	12	10	16
6.	F	47	3.5	1-2 times / month	12	14	14
7.	F	50	4.5	At least once a month	12	6	8
8.	M	26	3	1-2 times / month	12	4	0
9.	M	30	3.5	At least once in 2 months	12	6	6
10.	M	33	5	At least once a month	14	14	14

F= Female; M=Male

\*Parameters which were evaluated for calculating the total severity score included itching, vesiculation, oozing, crusting, fissuring, scaling

Table 4: Post treatment follow-up for 12 weeks (study group)

Sr. No.	Sex	Age (years)	Follow-up (weeks)						Blood report
			2	4	6	8	10	12	
1.	F	20	C	C	C	Itch +	Itch ++ Adv: LND, RxH	Itch -	WNL
2.	F	25	C	C	C	C	C	Itch +	WNL
3.	F	27	C	C	C	C	C	C	WNL
4.	F	35	C	C	C	C	C	C	WNL
5.	F	39	C	C	C	C	C	C	WNL
6.	F	42	Itch + Vesicle + Scaling + Adv: RxD	Itch + Vesicle - Scaling +	Itch -	C	C	Itch +	WNL
7.	F	45	C	C	C	C	C	C	WNL
8.	F	50	C	C	C	C	C	C	WNL
9.	M	18	C	C	Itch +	Itch ++ Adv: LND, RxH	Itch -	C	WNL
10.	M	22	C	C	C	C	Itch + Adv: LND	Itch -	WNL
11.	M	31	C	C	Itch +	Itch ++ Vesicle + RxD	Itch - Vesicle -	C	WNL

Adv =Advice; LND= Low Nickel Diet; F= Female; M=Male; WNL = within normal limit; C = Cleared; RxD = Treatment with disulfiram repeated for 1 week; RxH = Treated with oral antihistamine

nickel content is about 0.03 ppm of nickel.<sup>[9]</sup>

To date, several studies have been conducted by different scholars on treatment of hand eczema in individuals with nickel allergy using oral disulfiram and low nickel diet.<sup>[10,11]</sup>

Disulfiram or tetraethyl thiuram disulphide causes chelation of nickel. After oral intake, the drug is slowly and incompletely absorbed from the gut and metabolized slowly in the liver into diethyldithiocarbamate. The metabolite causes chelation of nickel from the body tissue and gets excreted from the body mostly through urine and in small amount in bile and sweat.

It is a fact that nickel cannot be avoided completely from diet; but careful selection of food with relatively low nickel concentration can bring a reduction in the total dietary intake of nickel per day. This can influence the outcome of the disease.

Kaaber *et al.*<sup>[11]</sup> observed the efficacy of oral disulfiram in a series of 11 nickel-positive patients with chronic dyshidrotic hand eczema (all these 11 patients showed flare-of-hand dermatitis after oral challenge with nickel sulfate). Seven patients had complete clearance

of hand eczema; improvement was noted in 2 other patients following disulfiram therapy. Dermatitis remained unchanged in 2 patients during the treatment period. Disulfiram was used in a dose of 200-400 mg daily for 4-10 weeks.

Christensen *et al.*<sup>[16]</sup> noted the efficacy of oral disulfiram in a series of 11 patients with nickel allergy and hand eczema. All the patients received disulfiram at a dose of 200 mg daily for a period of 8 weeks. He found that 2 patients with hand eczema healed completely and 8 patients improved considerably with disulfiram treatment. However, mild relapses were noted in all patients within a period of 2-16 weeks after stopping the treatment.

Kaaber *et al.*<sup>[13]</sup> again in a double blind placebo-controlled study treated 11 patients with hand eczema with disulfiram with a gradually increased dose up to a maximum of 200 mg/day for a period of 6 weeks. Five patients out of the 11 disulfiram-treated patients had complete healing of hand eczema during the treatment period as compared with 2 out of 13 patients in the placebo group.

Veien *et al.*<sup>[12]</sup> conducted a study where he advised low nickel diet to 90 nickel-sensitive patients. He

observed that 55 out of 90 nickel-sensitive patients who were advised low nickel diet for at least 4 weeks improved or were cleared of hand eczema. All these 90 patients had showed flare-of-hand dermatitis after oral challenge with nickel sulfate. Forty out of the 55 patients reported long-term improvement when followed up by a questionnaire 1-2 years later.

In this present study, effort was made to reduce the dietary intake of nickel by promoting LND to the patients. Effort was also made to deplete the already existing body nickel by giving oral disulfiram to the patients for 4 weeks.

At the end of 4 weeks of therapy, 10 (90.9%) patients in the study group had complete clearance of their hand eczema. While in the control group, only 1 patient had clearance of hand eczema. This difference was statistically very significant (at  $p$  value of 0.001). Majority of the patients used to have 1-2 attacks of relapse of hand eczema each month and had to use steroid or other immunosuppressives to control the problem. With disulfiram therapy and LND, 90.9% of these patients had complete clearance of their hand eczema and none of them had even a single relapse during the 4-week therapy.

Disulfiram was well tolerated by the patients. Patients experienced only a few and minor side effects. The major problem with disulfiram is its hepatotoxicity. There are reports of hepatotoxicity<sup>[11,13,16]</sup> following disulfiram therapy in patients with nickel sensitivity. But in those studies, disulfiram was administered for a longer time.<sup>[11,16]</sup> In this present study, as a pre-planned measure, disulfiram was administered only for 4 weeks; 2 patients received disulfiram for seven more days during the follow-up period. The purpose of such short-term (e.g., 4 weeks) treatment was to reduce the extent of liver damage; additional short course of disulfiram (e.g., 1 week) was administered when required.

Only 3 patients showed mild increase in the level of hepatic enzymes at the end of disulfiram therapy. Routine blood counts were within normal limits. When investigated again at the end of 12 weeks, all parameters were within normal limits.

The present study shows that combination of LND and oral disulfiram can bring a reduction in the clinical symptoms as well as in the recurrence rate of hand eczema in a nickel-sensitive individual. Therefore, low nickel diet and short course of oral disulfiram therapy can be considered as a good and safe option for the control of chronic, recurring hand eczema in nickel-sensitive individuals.

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