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Treatment of tinea pedis with socks containing copper-oxide impregnated fibers

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Abstract

Background: Tinea pedis, known as Athlete's foot, is a common fungal infection of the feet, the majority of cases caused by dermatophytes. Copper oxide has potent antimicrobial and antifungal properties.
Objective: A pilot study designed to examine the efficacy of treating tinea pedis utilizing copper-oxide impregnated fibers woven into socks worn on a daily basis.
Methods: Fifty-six patients, ranging in age from 21 to 85 years were clinically diagnosed, photographed, and treated with the copper soled socks. Eight variables were studied, including scaling, erythema, fissuring, burning or itching, vesicular eruptions, edema, odor, and drainage.
Results: In a 9-day average follow up, all patients showed improvement or resolution of erythema (with a 95% Confidence interval (CI) of 1.0), fissuring (CI = 1.0), vesicular eruptions (CI = 1.0), scaling (CI = 0.9–1.0) and for burning and itching (CI = 0.61–0.95). In a 40-day average follow up, the 95% CI for improvement or resolution of scaling was 0.68–0.97, for erythema, 0.65–0.97, and for fissuring, burning and itching and vesicular eruptions it was 1.0. None of the study subjects worsened or showed adverse reactions while wearing copper-oxide impregnated socks.
Conclusion: This study strongly supports the effectiveness in using copper-oxide impregnated polyester fibers in treating the common manifestations of tinea pedis.

Keywords: Tinea pedis; Copper oxide; Socks; Antifungal

1. Introduction

Copper ions, either alone or in copper complexes, have been used for centuries to disinfect liquids, solids and human tissue. Today copper is used as a water purifier, algaecide, fungicide, nematocide, molluscicide, and anti-bacterial and anti-fouling agent. Copper also displays potent anti-viral activity (see Ref [1]).

Several mechanisms for the biocidal activity of copper have been proposed. These include: denaturation of nucleic acids by binding to and/or disordering helical structures and/or by cross-linking between and within nucleic acid strands; alteration of proteins and inhibition of their biological assembly and activity; plasma membrane permeabilization; and membrane lipid peroxidation [1].

Microorganisms have developed several mechanisms to tolerate excess copper, such as exclusion of copper by a permeability barrier, intra- and extra-cellular sequestration of copper by cell envelopes, copper efflux pumps, and extracellular chelation or precipitation by secreted metabolites [1]. However, constant exposure to high copper concentrations is toxic to microorganisms and in contrast to the resistant microbes that have evolved to antibiotics in less than 50 years of use, resistant microbes to copper are extremely rare even though copper has been a part of the earth for millions of years. This lack of resistance may be explained by the capacity of copper to damage many key factors in microorganisms in parallel [1]. This lowers the probability for a particular microorganism to develop multiple mutations that may

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confer upon it complete protection from the various biocidal mechanisms of copper.

In contrast to the high susceptibility of microorganisms to copper, human skin is not sensitive to copper and the risk of adverse reactions due to dermal exposure to copper is extremely low [2]. Copper is considered safe to humans, as demonstrated by the widespread and prolonged use by women of copper intrauterine devices (IUDs) [3–5]. Copper is also permitted for use in fabrics by the USA Environmental Protection Agency (EPA).

Permanent or durable binding of inorganic compounds to organic substrates is extremely difficult, especially for mass production processes. Utilizing the properties of copper, a durable platform technology was developed, which introduces copper oxide to textile fibers, latex and other polymer products [6]. Recently we demonstrated that the copper-impregnated products possess a broad-spectrum of anti-microbial and anti-fungal properties, without causing skin sensitization or irritation [6,7]. This technology, for example, enables the production of anti-viral gloves and filters (which *inter alia* deactivate HIV-1 and other viruses), anti-bacterial and anti-fungal self-sterilizing fabrics (which *inter alia* kill antibiotic resistant bacteria, including Methicillin-resistant *Staphylococcus aureus* (MRSA) and Vancomycin-Resistant *Enterococcus* (VRE), *Tricophyton mentagrophytes* and *Candida albicans*) and anti-dust mite mattress-covers (which reduce mite-related allergies) [6,7].

About 15–20% of the population suffers from tinea pedis, a condition known also as Athlete's foot [8,9]. While there are many clinical presentations of tinea pedis, the most common manifestation occurs between the toes and on the soles, heels and sides of the foot. Although this fungal infection is not usually dangerous, it can cause discomfort, may be resistant to treatment, and may spread to other parts of the body or other people. Affected feet can also become secondarily infected by bacteria.

We hypothesized that introducing copper-oxide impregnated fibers into socks would be beneficial in preventing and treating tinea pedis (also referred to as athlete's foot) conditions. This manuscript describes the effectiveness of socks containing Cupron^{TM} copper-oxide impregnated fibers in alleviating and treating a variety of acute and chronic tinea pedis infections in patients, including diabetics and the elderly.

2. Methods

2.1. Socks

Socks (Copper Sole^{TM}), produced by the Renfro Corporation, were composed of 78% regular polyester fibers, 9% nylon fibers, 1% lycra fibers and 12% Cupron^{TM} copper-oxide impregnated polyester fibers. The weight/weight of copper oxide content per fiber was 1%. Hereafter these socks will be referred to as "copper socks". The same socks but without copper-oxide impregnated fibers served as control socks, and hereafter will be referred to as "control socks".

2.2. Fungicidal efficacy

Swatches of copper socks and control socks were tested quantitatively for anti-fungal activity according to the American Association of Textile Chemists and Colorists (AATCC) Test Method 100–1993. Briefly, sterile circular swatches of 4.8 ± 0.1 cm in diameter of both copper-containing and control socks were placed in Petri dishes and exposed to 1 ± 0.1 ml of a 24 h culture of the test fungi. After 24 h of incubation at 37 °C, each test sample was transferred to a bag containing 100 ml of saline and 0.1% of Tween 80. The bags were vigorously shaken for 2 min by using a Bag mixer (Stomager). Then 0.1 ml, 1 ml and 10 ml of the liquid from each bag was removed and added to saline containing 0.1% Tween 80 (final volume of 20 ml). Each of these samples was then passed through a 0.45 mm membrane (Millipore catalogue number EZHAWG474) by using a vacuum pump and a Gelman/Pall filtration device. The membranes were then washed twice with 20 ml of saline containing 0.1% Tween 80 to remove any possible remaining copper in the solution. The filters with the entrapped fungi were then put into a Petri dish containing selective culture media (6.5% Sabouraud Dextrose Agar in water for *Candida* and 3.9% Potato Dextrose Agar in water containing 0.025% Chloramphenicol for *Trichophyton*) and cultured for 48 (*Candida*) or 72 h (*Trichophyton*). The numbers of colonies formed were then counted. The exact number of fungi added to the samples in each experiment was determined by subjecting 3 test and control sock samples to the above procedure immediately after their exposure to the fungi ("0 hours" contact time). The usual titer per sample recovered was $\sim 0.5 \times 10^6$ fungi. The percent of fungi reduction was determined according to the following formula: $100(B - A)/B = R$, where R = %reduction; A = the number of fungi recovered from the inoculated test specimen swatches after 24 h; B = the number of bacteria recovered from the inoculated test specimen swatches immediately after inoculation ("0" minutes).

2.3. General design

Fifty six patients with severe athlete's foot symptoms were recruited to the study following their informed consent. The patients recruited in the study were patients that arrived to the Upstate Podiatry Clinic by their own initiative irregardless to the Trial. Most of the patients were enrolled on the basis of clinical diagnosis. In some cases this was confirmed with mycological determinations. When diagnosed with athlete's foot, they were asked if they would be willing to participate in the Trial. Six patients were given 2 pairs of regular socks for one week and then in the second week they were given 2 pairs of copper socks. The patients were instructed to use only the control socks given to them during the first week, and then during the second week to use only the copper socks.

All other patients were given only 2 pairs of copper socks. All patients were instructed to wear the socks daily as they would their usual hosiery and wash them regularly as they would with their own laundry. The patients were asked not to use any other treatments, such as moisturizing lotions, or over the counter or home remedies, or other socks, but only use the supplied socks during the study. The patients were examined throughout the study by the same expert (R.C.Z.) prior to receiving the control socks, prior to receiving the copper socks, and either one more time 8–10 days after starting to use the copper socks (short term follow-up) or several more times during a 21–44-day period after starting use of the copper socks (long term follow-up). Pictures were taken before and after treatment and the variables described below were monitored.

2.4. Variables

Eight measures were studied: erythema, burning and itching, edema, scaling, vesicular eruptions, fissuring, drainage, and odor. Scaling was present in all 56 patients, erythema in 51, fissuring in 37, burning or itching in 23, vesicular eruptions in 23, edema in 6, odor in 5 and drainage in 3 patients. There was a three level ordinal scale used: present, improvement, and resolved. Movement along this scale from "present" to "improved" or from either of the first two to "resolved" was considered a positive sign. Movement the other way, from "improved" to "present", was considered a negative sign. Improvement was graded as the visual lightening of erythema, decrease in scaling, absence of odor, decrease in swelling, and the patient's own declaration of decreased itching and/or burning. Resolved implied the absence of previously observed or patient reported signs and symptoms. The status of all variables in all patients in all examinations was determined by the same examiner (R.C.Z.).

All patients were evaluated 8–10 days after wearing the copper oxide containing socks. Randomly selected patients were included for a long term follow-up and were evaluated a second time (at 21–44 days after using the copper socks). If a patient was considered resolved for a particular variable on the first visit after wearing the socks (at 8–10 days of short term follow-up), that individual could at best be scored a "same" for that variable at the long-term follow-up. Therefore, "same" could be equally considered to be "holding improvement". The average length of time in the long term section was defined as being the time between the first visit and the date when the last comment was made about the patient. Only patients who had a specific problem at the outset of the study were counted later.

2.5. Statistics

One sample proportion tests and exact binomial tables were used with Minitab software (Minitab Inc. State College, PA, U.S.A.) or from Conover's Practical Nonparametric Statistics [10], in order to analyze the data.

We defined Π as the true proportion of *all* patients anywhere who were improved/resolved with the use of copper oxide containing socks. Since we cannot know this proportion, we sampled using the 56 patients described (i.e. the proportion of the sample, p, was used as an estimate of Π). While not a random sample, there was no reason to assume the patients we treated were significantly different from other patients with these conditions. We computed the percentage of improved/resolved. Using this proportion, we computed 95% confidence intervals for a single proportion, using an exact interval for those instances where the sample size was <30.

3. Results and discussion

The biocidal efficacy of the unlaundered socks and socks laundered up to 30 times was determined against *Tricophyton mentagrophytes*, *T. rubrum* and *Candida albicans*, microorganisms frequently involved in athlete's foot infections. As depicted in Fig. 1, both unlaundered and laundered socks were highly efficacious against all three tested fungi. This is in accordance with previous studies [6,7]. We thus subsequently tested the hypothesis that using socks containing polyester fibers impregnated with copper oxide would be beneficial in treating tinea pedis.

Fifty six patients (17 women and 39 men) suffering from tinea pedis were enrolled in the study following their informed consent. Average age of the group was 58 with a standard deviation of 16 years (range 21–85 years). Twenty-one were diabetic and twenty-one were older than 65. Twelve patients had "moccasin" type of tinea pedis infection only, 2 had interdigital tinea pedis only and 42 had interdigital tinea

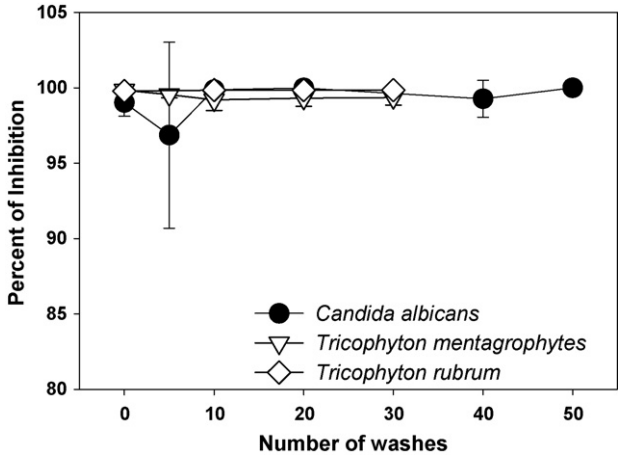

Fig. 1. In vitro testing of the biocidal potency of the socks, new and following home laundry. The biocidal potency of the socks was tested by an independent laboratory (AminoLabs, Rehovot, Israel) by using the American Association of Textile Chemists and Colorists (AATCC) test method (TM) 100. The socks were washed following the AATCC TM 150. *Candida albicans*, *Tricophyton rubrum* and *Tricophyton mentagrophytes* were exposed to the socks for 24 h. The results are the mean and standard deviation of three separate experiments for each microorganism.

pedis in combination with moccasin type tinea pedis. Forty three patients suffered from chronic tinea pedis (years) while 13 suffered from acute tinea pedis (weeks to months) at the time of enrollment. Six months prior to enrollment in the trial and during the trial (from September 2004 until January 2005) none of the patients were receiving topical or oral anti-fungal or topical or oral steroid agents. Two type II diabetic patients received concurrent antibiotics during the study (10 day regimen) for treatment of ulcers that became bacterially infected. The first patient, who suffered from a bilateral hallux ulcer that became infected with methicillin resistant *Staphylococcus aureus* (MRSA), was treated with 600 mg Zyvox (1 pill every 12 h). The second patient, who suffered from a lateral malleolar ulcer that became infected with *Staphylococcus aureus* coagulase negative, was treated with 500 mg Keflex (1 pill four times a day). Both ulcers were treated directly by sharp debridement (surgical removal of nonviable tissue), Allevyn Wound Management Dressings, Smith & Nephew, London, UK (a dressing designed to absorb the wound exudates, without drying out the wound), and Regranex Gel, Johnson & Johnson, NY, USA (a gel containing platelet-derived growth factor, a natural substance that helps wound healing). These treatments as well as the oral antibiotics should not have compromised the study as they are not indicated for treatment of the common infectious organisms of tinea pedis. The patients with long term tinea pedis had previously tried over the counter anti-fungal creams and ointments, foot soaks, and foot powders with limited success.

Initially the first 6 patients enrolled in the study were given control socks containing no copper (control socks) and were asked to wear them daily for a week. The patients were then examined and given copper-oxide containing socks (hereafter referred to as "copper socks"), and asked to use only the copper socks thereafter for an additional week. Analysis of the results obtained with these 6 patients showed that there was no change in the variables examined after using the control socks. In contrast, there was a clear trend of improvement or resolution in all variables studied following the patients' switch to using the copper socks (Table 1).

Untreated patients with these conditions seldom improve [11], and as described above, these patients suffered from tinea pedis for months to years, prior to the trial. Since the control socks had no effect (as expected), but there was a clear improvement following the use of the copper socks, we decided based on ethical considerations to give only copper socks to the rest of the study participants. We decided to look at what happened to these patients who were treated compared to what would have occurred had they not been treated. We used a dichotomous outcome: improved/resolved vs. not improved/resolved.

In 55 out of the 56 patients who suffered from scaling there was a significant improvement within an average follow-up of 9 days, and in 5 there was a resolution of scaling (95% confidence interval (CI) for improvement and resolved = 0.9–1.0). Likewise, again over an average period of 9 days of follow-up, in all 51 patients suffering from erythema there was an improvement, including complete resolution of erythema in 22 patients, (CI = 1.0). Similarly to scaling and erythema, during the same time frame there was a clear improvement or resolution in fissuring, burning and itching, and vesicular eruptions (CI = 1.0; 0.61–0.95; and 1.0, respectively) in the patients studied, with the exception of 4 patients that reported no change in the burning or itching (Table 2). The number of patients suffering from edema, odor and drainage was too small to draw any conclusions based on statistical analysis, however, evident improvements were noted (Table 2).

Patients, in whom no resolution of a variable studied was noted on the short term follow-up, were randomly included in the long term follow-up. These patients were instructed to continue using the copper socks daily. Similarly to the short term follow-up, there was a clear improvement or resolution of the various variables studied in the long term follow-up, with CI of 0.68–1.0; 0.65–0.97; 1.0; 1.0; and 1.0 for scaling, erythema, fissuring, burning and Itching, and vesicular eruptions, respectively (Table 2). Representative examples of resolution of erythema, scaling, fissuring and vesicular eruptions are shown in Fig. 2. Since the number of patients suffering from edema, odor, and drainage was too small, these patients were not followed long term. In some cases a relapse

Table 1
Preliminary follow-up of six patients that received control and Copper Sole™ socks

	Variable				
	Scaling 0/1/2[a]	Erythema 0/1/2[a]	Fissuring 0/1/2[a]	Burning or itching 0/1/2[a]	Vesicular eruptions 0/1/2[a]
Patient 1	P/P/I	P/P/I	P/P/I	P/P/R	P/P/I
Patient 2	P/P/I	N/N/N	N/N/N	P/P/R	P/P/R
Patient 3	P/P/I	P/P/R	P/P/I	N/N/N	P/P/I
Patient 4	P/P/I	P/I/R	N/N/N	N/N/N	N/N/N
Patient 5	P/P/I	P/P/R	P/P/R	N/N/N	P/P/R
Patient 6	P/P/I	P/P/R	P/P/R	N/N/N	P/P/R

Scaling, erythema, fissuring, burning or itching, and vesicular eruptions were examined prior to the commencement of the study (0) and then after the use of the control socks for one week (1) and after the use of the Copper Sole™ socks for one week (2). P—positive (present) for the variable examined; I—improved in comparison to the previous assessment; R—resolved; N—negative for the variable examined.

[a] Week.

Table 2
Summary of variables of the short and long term follow-ups

Variable	Short term follow-up						Long term follow-up					
	n[a]	S/W[b]	Impr[c]	Res[d]	d[e]	CI[f]	*n*	S/W	Impr	Res	d	CI
Scaling	56	1	50	5	9	0.9–1	24	2	13	8	34	0.68–0.97
Erythema	51	0	29	22	9	1.0	22	3	12	7	36	0.65–0.97
Fissuring	37	0	22	15	10	1.0	17	0	11	6	39	1.0
Burning or itching	23	4	5	14	8	0.61–0.95	8	0	0	8	46	1.0
Vesicular eruptions	23	0	10	13	9	1.0	10	0	4	6	45	1.0
Edema	6	2	3	1	8	–[g]	–	–	–	–	–	–
Odor	5	0	3	2	8	–	–	–	–	–	–	–
Drainage	3	0	1	2	9	–	–	–	–	–	–	–

[a] *n*, total number of patients.
[b] S/W, number of patients with same or worst symptoms.
[c] Impr, number of patients with improved symptoms.
[d] Res, number of patients resolved.
[e] d, average days of follow-up.
[f] CI, 95% confidence interval for improvement and resolved.
[g] Not determined/examined.

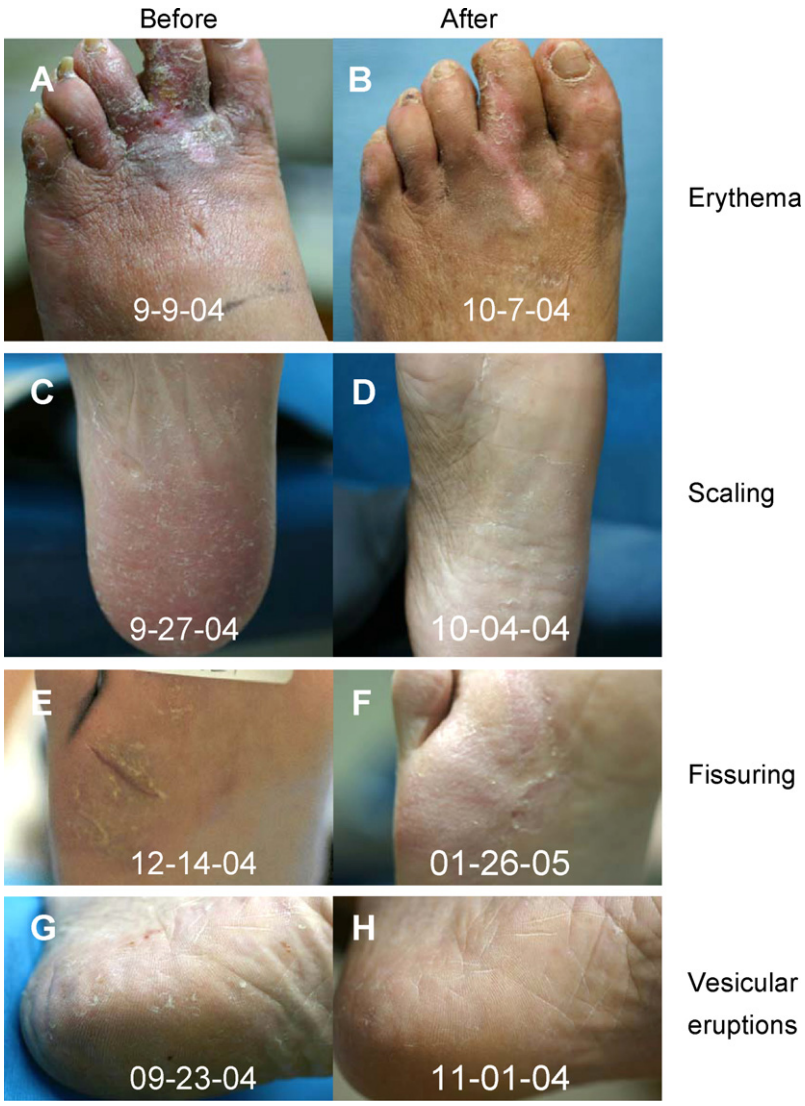

Fig. 2. Resolution of erythema (A and B), scaling (C and D), fissuring (E and F) and vesicular eruptions (G and H) following the usage of the copper-oxide containing socks. The panels for each patient are pictures taken before (A, C, E, and G) and after using the copper-oxide containing socks (B, D, F and H).

in the tinea pedis conditions was observed. Relapsing of tinea pedis can be related to a number of host factors including: discontinuing usage of the copper oxide containing socks, wearing the socks only sporadically, wearing contaminated shoe gear, and continued pedal exposure to conducive environmental factors favoring fungal organism growth. In no instance, however, did a patient who had no specific problem develop one.

Considering that there was no improvement in these measures for many months prior to the trial in these patients, it can be concluded that there is credible medical evidence that the usage of socks containing copper-oxide impregnated fibers is effective in improving or resolving erythema, scaling, fissuring, burning and itching, and vesicular eruptions. Moreover, since nearly 40% (19 of 51) of the group was either diabetic or older than 65 (10 were both diabetic and older than 65 years), these results may be generalized to patients with diabetes, including elderly diabetics. None of the study subjects worsened or showed adverse reactions while wearing copper-oxide impregnated socks.

Although the findings of this pilot study clearly support to the notion that using socks containing copper impregnated fibers may be useful in treating pedal fungal infections, both "moccasin" and interdigital type of tinea pedis, without the need of additional conventional treatment, further studies should be carried out. These studies should be randomized to include two large groups of individuals, one receiving the copper socks and the other receiving identical socks but not containing copper oxide (control socks). These studies should ideally be double blinded and should also include mycological determinations before and after the use of the control and copper-oxide impregnated socks.

Conflict of interest

Gadi Borkow is the Chief Medical Officer of Cupron, the company that produces the polyester fibers impregnated with copper that were introduced into the socks tested for their effect on tinea pedis. Richard C. Zatcoff is an independent podiatrist and Michael S. Smith is an independent medical statistician.

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