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Reducing the risk of skin pathologies in diabetics by using copper impregnated socks

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SUMMARY

Diabetic individuals frequently suffer from skin pathologies, especially in their feet. Co-existing peripheral vascular disease and neuropathy exacerbate the capacity of these individuals to cope with infections, minor cuts and wounds, often leading to hard to treat and chronic ulcers.

Copper has potent anti-fungal and antibacterial properties. Copper is also an essential trace element vital for the normal function of many tissues and indispensable for the generation of new capillaries and skin. Human skin is not sensitive to copper and the risk of adverse reactions due to dermal exposure to copper is extremely low.

We hypothesize that part of the increased risk of developing foot skin pathologies in diabetic patients with compromised blood circulation to the foot is due to low local copper levels. We further hypothesize that copper ions released from copper impregnated socks and absorbed through the skin would improve the well-being of the skin of diabetic patients by inducing angiogenesis and expression and stabilization of extracellular skin proteins, in addition to their biocidal effect of reducing the risk of fungal and bacterial infection of the diabetic foot . Thus, the use of copper impregnated socks may be used as a preventive modality. Furthermore, we hypothesize that the copper released from the socks may even be beneficial in the healing of cuts, wounds and even hard to treat skin pathologies.

Skin infections of the diabetic foot

Various studies suggest that the majority of diabetic patients will suffer a skin disorder during the course of their disease and for some, skin changes may even precede the diagnosis of diabetes [1]. The most common manifestations include fungal and bacterial skin infection, nail disease and diabetic dermopathy. Other less commonly observed conditions include rash with reddish bumps, reddening of the soles, vesicles and ulcers.

Fungal infection, although relatively inconspicuous, is a very common foot problem in diabetics. People with diabetes are nearly 3–5 times more likely to develop onychomycosis (nail infection) and tinea pedis (skin infection), respectively [2,3].

Fungal infection virtually always begins on the skin on the sole of the foot and spreads to other parts of the foot. The inter-digital areas of the foot can also harbor infections. Typically, fungal infection produces little in the way of symptoms and often goes unnoticed, mistaken for dry skin, as the normal epidermal skin water content of ∼15% drops and the skin becomes dry and loses resilience. This dry skin condition, which is common in diabetic patients, predisposes an individual to fissuring and cracking of the epidermis which, in turn, can lead to secondary infections of the foot. This is further aggravated by the neuropathy that is common in many diabetic patients. Thus, fungal infections, when left untreated, reduce skin integrity and leave it vulnerable to secondary infection through fissures and splits and to the spread of the bacterial infection to just below the skin surface. Once past the skin surface, the warmth, moisture and nutrients allow bacteria to grow rapidly. Disease-causing bacteria release enzymes which cause tissue damage. The body's reaction to damage is inflammation which is characterized by pain, redness, and swelling. This red, painful region grows bigger as the infection and resulting tissue damage spread. An untreated infection may spread to the lymphatic system, the lymph nodes and the bloodstream, or into deeper tissues. Furthermore, dermatophytes may spread from the foot to the hands and groin. Management of fungal disease is often considered difficult due to high relapse and re-infection rates.

The key feature of all types of diabetes is the high concentration of glucose in the blood, which results in a number of changes in the cellular biochemistry. While the extent and effects of the cellular biochemical changes may vary between individuals, alterations in collagen synthesis and structure and abnormal blood flow due to the development of lesions in small blood vessels throughout the body may ultimately make the skin vulnerable to infection due to a suppressed immune response. Alone, or in combination, each of these may contribute to the pathology of skin disease.

It is estimated that ∼30% of diabetic patients have skin lesions on the foot [4] and that the risk of developing a foot problem

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doubles in a diabetic individual [1]. Co-existing peripheral vascular disease has been identified as a risk factor [5]; microangiopathic disease in common in diabetic patients [6].

Thus, taken together, the risk of infection in the diabetic foot is high due to reduced skin integrity, lack of sensory perception and poor peripheral circulation, which reduces the capacity of the immune system to respond efficiently to an infection. Accordingly, patients with diabetes have an increased risk of developing cellulitis [7] and are likely to require longer hospitalizations than their non-diabetic counterparts [8]. Since skin infections remain a major threat to the diabetic foot, the prevention of minor infections could ultimately prevent the development of more major and complicated infections, which can lead to severe complications, especially in diabetics.

Copper impregnated socks and the diabetic foot

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 antibacterial and anti-fouling agent. Copper also displays potent anti-viral activity [9].

Constant exposure to high copper concentrations is toxic to microorganisms. In contrast to the antibiotic and other drug-resistant microorganisms that have evolved in less than 50 years of use, resistant microorganisms to copper are extremely rare even though copper has been a part of the earth for millions of years. This resistance may be explained by the capacity of copper to damage many key factors in microorganisms in parallel [9]. This lowers the probability for a particular microorganism to develop multiple mutations conferring complete protection against the various biocidal mechanisms of copper.

Copper is an essential trace element needed for the normal function of many tissues, including the skin and the immune and blood systems [10], and its recommended daily allowance is 1 mg [11]. Exposure to copper is considered safe to humans, as demonstrated by the widespread and prolonged use by women of copper intrauterine devices (IUDs) [12–14] and over-the-counter wound healing treatments containing copper [15,16]. Human skin is not sensitive to copper and the risk of adverse reactions due to dermal exposure to copper is extremely low [17,18].

Copper can be permanently introduced into textile fibers from which textile products can be made [19,20]. The copper impregnated products possess a broad-spectrum of anti-microbial and anti-fungal properties, without causing skin sensitization or irritation [19,20]. Copper oxide impregnated socks have been shown to be effective in treating a variety of acute and chronic tinea pedis (also referred to as athlete's foot) infections in patients, including diabetics and the elderly [21]. Fig. 1 demonstrates many examples of improvement or resolution of tinea pedis infections solely by the use of copper oxide containing socks.

While the significant improvement or resolution in tinea pedis in the diabetic patients studied is due to the biocidal properties of copper against fungi and bacteria, which play a key role in the development of tinea pedis and skin pathologies, there may be other reasons for the beneficial effect of copper containing socks in preventing and treating tinea pedis in diabetic patients, as discussed below.

As stated, copper is an essential trace element involved in numerous human physiological and metabolic processes [10], including skin formation [22,23] and wound repair [24], as may be seen in the following examples. Several copper dependant enzymes and polysaccharides, such as lysyl oxidase, metalloproteinases, glycosaminoglycans and small proteoglycans, needed for cell

Fig. 1. Resolution or improvement of tinea pedis infections following the usage of the copper-oxide containing socks.

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Fig. 2. Wound closure following the usage of copper-oxide containing socks.

proliferation, re-epithelization and extracellular matrix protein crosslinking, including of collagen, elastin and fibronectin, require copper as a cofactor [23,25,26]. The copper dependant superoxide dismutase enzyme, important in protection against free radicals, is present in the skin [27]. Stabilization of fibronectin mats [28,29] and collagen crosslinking is increased by copper ions [30]. Copper modulates integrins expression by keratinocytes [31]. Topical copper sulphate treatment has been shown to accelerate epithelial tissue growth [32]. Furthermore, copper has been shown to stimulate angiogenesis [33] by inducing generation of vascular endothelial growth factor (VEGF) [32]. Human peptide Gly-(L-His)-(L-Lys) or GHK, which has a very high affinity for Cu^{2+} and forms a GHK-Cu chelate, stimulates protein synthesis of collagen and elastin, angiogenesis and wound repair [22]. We also found that copper ions released *in situ* from wound dressings induced upregulation of many proangiogenic and other key factors involved in angiogenesis, skin regeneration and wound healing (manuscript submitted for publication). Importantly, the absorption of copper or copper oxide through skin has been demonstrated [18,34].

Our hypothesis

We hypothesize that part of the increased risk of diabetic patients, who might have compromised circulation to the foot, to develop foot skin problems is due to low local copper levels. Furthermore, we hypothesize that the humidity present in the skin and within a shoe facilitates the release of copper ions from socks impregnated with insoluble copper oxide. These copper ions, in addition to acting as a biocide that reduces the risk of fungal and bacterial infection of the diabetic foot, are absorbed through the skin and thus improve the well-being of the skin of diabetic patients by inducing angiogenesis and expression and stabilization of extracellular skin proteins. The capacity of copper to increase the stability and integrity of the skin would reduce the risk of skin rupture and secondary skin infection by pathogenic bacteria in the diabetic foot. Furthermore, it may be that the absorption of copper through the skin in the foot would enhance blood circulation in the foot, the effectiveness of the immune system and the overall capacity of the diabetic individual to cope with fungal and bacterial infections.

Venous and diabetic foot ulcers are among the most often occurring chronic wounds [35], affecting nearly two million people annually, and possibly leading to impaired mobility and amputation [36]. Preventing foot infection and skin rupture, as well as increasing blood circulation, would significantly reduce the risk of wounding. Moreover, as we observed in a few individuals with open wounds who have used copper impregnated socks, the release of copper ions from the socks resulted in wound healing, including in diabetic individuals suffering from chronic ulcers, as shown for such a case in Fig. 2.

In conclusion, we hypothesize that in diabetics with poor peripheral blood circulation, the exterior supplement of copper eluting from copper containing socks would result in reduced risk of skin rupture and infection and improved capacity of the diabetic individual to cope with fungal and bacterial infections. Furthermore, it would improve effective healing of minor wounds and cuts, thus preventing deterioration that may lead to hard to treat severe and chronic lesions.

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