Biol Trace Elem Res (2012) 150:3–9
DOI 10.1007/s12011-012-9479-5

Selenium and Psoriasis

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Received: 4 June 2012 / Accepted: 11 July 2012 / Published online: 24 July 2012

Abstract Psoriasis is a chronic, immune-mediated skin disease characterized by production of reactive oxygen species due to the activation of tumor necrosis factor alpha (TNF-α), which is thought to be an important factor in inducing and maintaining psoriatic lesions. As an external factor, ultraviolet B (UVB) radiation stimulates TNF-α production and secretion by human keratinocytes in vitro and can also reach the upper dermis and suppress endothelial cells in vitro. The selenium level in psoriatic patients has been found to be lower than expected, but studies on its role in the pathogenesis of the disease are scarce. Selenium can influence immune response by changing the expression of cytokines and their receptors or by making immune cells more resistant to oxidative stress. It was reported that selenium supplementation had inhibitory effects on TNF-α levels in patients with psoriasis, but the details are not completely elucidated. Selenium compounds are also known to prevent the in vitro release of UVB-induced proinflammatory cytokines by inhibition of mRNA in human keratinocytes. In the present review, the protective role of selenium in oxidative stress, lesions, and immune system regulation in patients with psoriasis is summarized.

Keywords Selenium · Selenoprotein P · Tumor necrosis factor alpha · Oxidative stress · Skin · Psoriasis

Abbreviations

GSH-Px	Glutathione peroxidase
GSH	Glutathione
PUFAs	Polyunsaturated fatty acids
ROS	Reactive oxygen species
SOD	Superoxide dismutase
MDA	Malondialdehyde
PASI	Psoriasis area and severity index

Introduction

Psoriasis is a chronic and relapsing disorder affecting 1–3 % of the world's population. It results from the interaction between genetic predisposition and a large spectrum of environmental factors that trigger the development of skin lesions [1]. The role of lifestyle habits, such as smoking, diet, and alcohol consumption, has been given considerable attention in recent years. Alcohol consumption is supposed to be one of the risk factors for the disease and also may be associated with the course of psoriasis and influence its treatment [2]. The metabolism of ethanol contributes to lipid peroxidation and reduction of natural antioxidants, thus enhancing the toxic effects of free radicals. An impaired antioxidant skin barrier may result in a rise of free oxygen radicals in psoriatic plaques [3].

Some oxygen metabolites are highly reactive, whereas others, such as hydrogen peroxide, are less reactive and have the ability to diffuse easily across the cell membranes.

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They may, therefore, impose oxidative modifications upon the membrane. After reaching the inside of the cells, they will trigger the cellular antioxidant defense mechanisms. Oxidative stress develops within the cells after its defenses are depleted, and oxidative modifications will be evident [4].

Increased reactive oxygen species (ROS) and lipid peroxidation have an important role in the inflammatory process. As such, they are seen in many dermatologic disorders, for example, atopic dermatitis [5], psoriasis [3, 6], vitiligo [7], acne vulgaris, pemphigus vulgaris [8], and alopecia areata [9].

Selenium is known to have immune-modulating and antiproliferative properties [10]. It can influence immune response by changing the expression of cytokines and their receptors or making immune cells more resistant to oxidative stress [3, 6]. The antiproliferative properties of selenium compounds are related directly to their toxicity [1, 3]. As an integral part of thioredoxin reductases and other antioxidant enzymes, such as glutathione peroxidases [11], selenium participates in protection of the skin against harmful environmental factors, e.g., in the prevention of ultraviolet-induced cell damage and death. On the other hand, it has been demonstrated that selenite and selenocystamine could induce apoptosis in keratinocytes because of their prooxidant catalytic activity [12]. Current data about changes of selenium concentration and activity of selenium-dependent enzymes in blood of patients with psoriasis are contradictory [3].

In humans, low selenium status has been associated with up to a fourfold increased risk of developing skin cancer [13]. Both glutathione peroxidase (GSH-Px) and thioredoxin reductase enzymes have been implicated in protection from ultraviolet radiation-induced damage, one of the major risk factors for skin cancer [14, 15]. The importance of the chemical form of selenium that is administered is underlined by the fact that inorganic forms of selenium, such as sodium selenite, are more rapidly incorporated into selenoproteins than the chief nutritional form, L-selenomethionine [16]. Stewart et al. have shown that L-selenomethionine can act as a prooxidant and cause oxidative DNA damage [17]. The anticarcinogenic effects of selenium and optimal GSH-Px activity in humans and animals sometimes require daily selenium intakes that are above the recommended daily allowance [18].

Psoriasis and Oxidative Stress

The human body is equipped with a complete arsenal of defenses against external and internal aggressions. Those against ROS, such as superoxide, peroxide, and hydroxyl radical, are crucial in inflammatory responses, where they participate in physiological processes, such as the arachidonic acid cascade and phagocytosis [19, 20]. The concentrations of ROS are kept under strict control by the activity of a complex defense system including antioxidant enzymes, such as superoxide dismutase and GSH-Px, and by nonenzymatic species like vitamins C, E, A, or β-carotene [21].

There is a large body of evidence that poly- and mononuclear phagocytes are crucially involved in host defense (Fig. 1). In addition to eliminating circulating immune complexes, debris, and necrotic cells, they effectively attack invading microorganisms. Monocytes and macrophages have additional important functions as antigen-presenting and cytokine-releasing cells, whereas polymorphonuclear phagocytes are considered to represent the first line of defense in terms of ingesting and killing potential pathogens [22]. During particle ingestion, granulocytes and macrophages produce large amounts of highly reactive molecules, mainly oxygen radicals, thus leading to a significant increase in energy and oxygen consumption. The sharp rise in consumption of molecular oxygen during phagocyte activation does not reflect an increase in aerobic energy production as primarily assumed (a "respiratory burst"), but is the result of an increased generation of highly reactive oxygen species [23].

Neutrophils and other phagocytes manufacture superoxide by the one-electron reduction of oxygen at the expense of NADPH. Most of the superoxide radical reacts with itself to form hydrogen peroxide [24]. From these agents, a large number of highly reactive antimicrobial oxidants are formed, including hypochlorous acid, which is produced by the myeloperoxidase-catalyzed oxidation of Cl^- by H_2O_2; hydroxyl radical ($OH^·$), produced by the reduction of H_2O_2 by Fe^{2+} or Cu^+; peroxynitrite ($ONOO^-$), formed by the reaction between O^{2-} and NO^-; and many others [25]. These reactive oxidants are manufactured for the purpose of killing invading microorganisms, but they also inflict damage on nearby tissues and are thought to be of pathogenic significance in a large number of diseases including psoriasis [17, 26].

The skin acts as an interface between the human body and its surrounding environment, thus the skin is constantly exposed to both endo- and exogenous prooxidants, leading to the generation of harmful oxidant species. Oxidative stress and the generation of excessive free radicals have been related to skin inflammation in psoriasis. Patients with this condition have reduced plasma levels of β-carotene and α-tocopherol as well as a decline in serum selenium and high concentrations of malondialdehyde, a marker of lipid peroxidation in the plasma and red blood cells [6, 27, 28]. There are literature reports that suggest that topical application or oral administration of antioxidants, such as vitamin E and selenium, is suggested as preventive therapy for the psoriasis [6, 29].

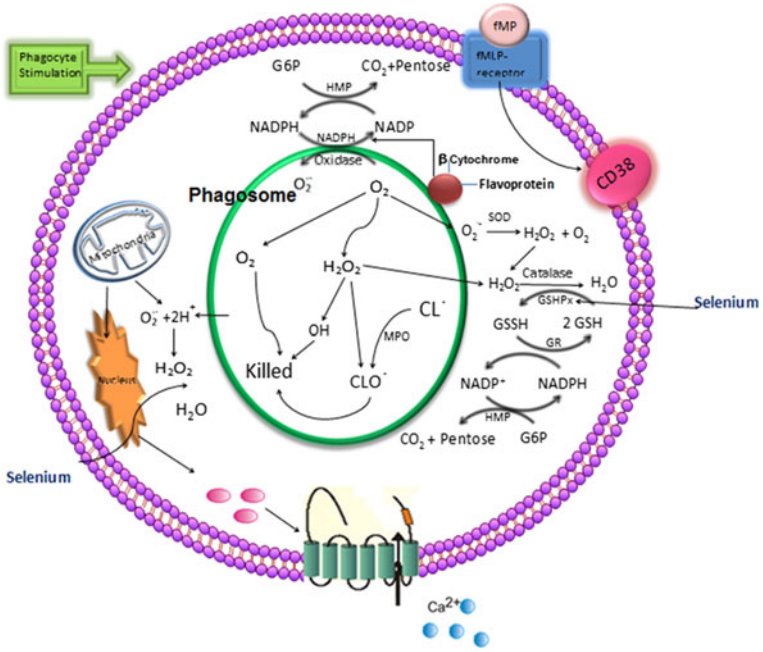

Fig. 1 There is a large body of evidence that poly- and mononuclear phagocytes are crucially involved in host defense. Neutrophils and other phagocytes manufacture superoxide by the one-electron reduction of oxygen at the expense of NADPH through hexose monophosphate pathway. Most of the superoxide radical reacts with itself to form H_2O_2 [24]. From these agent, a large number of highly reactive microbicidal oxidants are formed, including hypochlorous acid, which is produced by the myeloperoxidase-catalyzed oxidation of chloride (Cl^-) by H_2O_2; hydroxyl radical ($OH^·$), produced by the reduction of H_2O_2 by Fe^{+2} or Cu^+; peroxynitrite ($ONOO^-$), formed by the reaction between O^{-2} and NO^-; and many others [25]. These reactive oxidants are manufactured for the purpose of killing invading microorganisms, but they also inflict damage on nearby tissues, and are thought to be of pathogenic significance in a large number of diseases including psoriasis [17, 26]

Selenium and Skin Diseases

Selenium is present in about 40 selenium proteins in humans. As selenocysteine, it functions in a redox center that reduces the likelihood of propagation of oxidative damage to lipids, lipoproteins, and DNA. Adequate selenium intake is important for normal humoral and cell-mediated immunities [30]. Dietary or in vitro supplementation with selenium results in an earlier expression of high-affinity interleukin-2 receptor on the surface of concavalin A-stimulated lymphocytes [31]. Inorganic selenium salts induce inhibitory effects on inflammatory cytokine production: interleukin-1α, interleukin-6, and tumor necrosis factor alpha (TNF-α) in vitro [32].

Fourteen years ago, a large-scale study showed for the first time that the selenium concentration in psoriasis patients is lower than in healthy subjects [33]. Several investigators subsequently confirmed this finding. Disturbances in keratinization, leading to excessive loss of trace elements with desquamation, malabsorption, or tissue distribution abnormalities, were suggested as explanations of this phenomenon. Oral selenium supplementation as an adjuvant therapy in psoriasis patients was investigated. L(+)-Selenomethionine is thought to be the most appropriate oral supplemental form of selenium because it binds more than 80 % of the total selenium in seleniferous corn or wheat and provides all forms of bioactive selenium needed for selenium protein biosynthesis in humans. This organic form is often preferred in interventions because of its good bioavailability and insignificant acute toxicity [34].

Selenium has also protective effects against ultraviolet-induced oxidative DNA damage, cell death, and apoptosis in cultured skin cells. In addition, selenium enhances immune function in humans and animals, protects humans against certain forms of cancer, and protects mice against ultraviolet-induced skin cancers; expression of phosphorylated p53, Fas, Bcl-2, Bax, oxidized guaninosine, and CD1a was assessed by immunohistochemistry [35]. Selenium salts and selenoprotein participate in protection of the skin against harmful environmental factors, in tanning and prevention of ultraviolet-induced cell damage and death. However, it has been demonstrated that selenite and selenocysteine can induce apoptosis in keratinocytes due to prooxidant catalytic activity. A low selenium concentration and depressed selenium-dependent enzyme activity were observed in patients with inflammatory skin disorders, skin cancers, malignant melanoma, and epidermotropic cutaneous T cell lymphomas [3].

Psoriasis and TNF-α

Psoriasis vulgaris is a common chronic inflammatory cutaneous disease resulting from interactions between genetic predispositions and triggering environmental factors, such as oxidative stress [3]. Narrow-band ultraviolet B irradiation is frequently the treatment of choice in mild to moderate cases of psoriasis vulgaris. Its therapeutic effects involve several mechanisms, including the induction of anti-inflammatory and immunosuppressive cytokines.

The activation of the inflammatory cells in psoriasis may result in increased leukocyte activation products in the peripheral blood, which may induce oxidative and proteolytic modifications to plasma constituents and neighboring cells, such as circulating erythrocytes. Considering that the erythrocytes have a very limited biosynthesis capacity, physical and/or chemical damage will accumulate throughout its life span.

TNF-α is a cytokine that plays a crucial role in the pathogenesis of psoriasis, mainly by inducing the expression of vascular cellular adhesion molecule-1 or E-selectin on dermal microvascular endothelium. The action of TNF-α is mediated by two receptors of molecular weights 55 and 75 kD. Soluble forms of these receptors may bind the cytokine, thus competing with the cell surface receptor or stabilizing the cytokine molecule. Increased concentrations of TNF-R1 in patients with psoriasis compared with those in healthy subjects have been described [12].

Selenium Deficiency and Psoriasis

The selenium concentration in psoriasis patients is lower than that of healthy individuals, but there are few studies on its role in the pathogenesis of the disease [13–16]. An impaired antioxidant barrier in skin may result in a rise of free oxygen radicals in psoriatic plaques. Thionine may modulate immunologic mechanisms of the disease by increasing the number of $CD4^+$ T cells in reticular dermis within psoriatic plaques [17]. Previously published preliminary results of Serwin et al. [3, 18] showed that selenium concentration and selenium-dependent GSH-Px activity in erythrocytes are higher in males with psoriasis, lasting no longer than 10 years than in those with the disease lasting 3 years or more (Table 1).

Kadry and Rashed, using plasma and tissue samples from 20 patients with psoriasis and 10 healthy controls, investigated the levels of overexpression of osteopontin and selenium in psoriasis, and their relation to metabolic status in patients to identify a possible link between these markers and comorbidities observed. They observed that the plasma selenium levels were lower in patients with psoriasis than in controls and concluded that overexpression of osteopontin and low plasma selenium levels are predictable factors for occurrence of psoriasis [36].

Serwin et al. [37] examined the influence of selenium supplementation on the efficacy of narrowband ultraviolet B (UVB) treatment in patients with psoriasis and studied the correlation between serum concentrations of selenium, sTNF-R1, and C-reactive protein (CRP) during treatment in these patients. They treated 37 patients by administering 200 μg Se/day as thionine or placebo in addition to UVB therapy five times a week. The patients were evaluated by measuring the psoriasis area, severity index, and serum concentrations of selenium (in micrograms per liter), sTNF-R1 (in nanograms per milliliter), and CRP (in milligrams per liter) at the start of treatment and at 2 and 4 weeks of treatment as well as 1 month after the end of treatment. Their results confirm that the sTNF-R1 and CRP concentrations were elevated in active psoriasis, and that 1-month supplementation with thionine does not help as adjuvant therapy in patients with psoriasis [37].

McKenzie et al. [38] and Rafferty et al. [39] reported low serum selenium levels in patients with psoriasis, and that

Table 1 Selenium levels are low in patients with psoriasis

Reference	Patient and material	Year	Patient number
Michaelsson et al. [33]	Adult and whole blood and plasma	1989	113
Fairris et al. [47]	Adult and blood	1989	69
Donadini et al. [43]	Adult and plasma Adult and whole blood	1992	64
Serwin et al. [3]	Adult and plasma and erythrocytes	2002	Groups 1–35 Groups 2–42
Serwin et al. [28]	Children and erythrocyte	2003	30
Serwin et al. [34]	Adult and plasma	2003	22
Serwin et al. [37]	Adult and serum	2006	37
DeSilva et al. [35]	Adult and blood	2007	7
Kadry and Rashed [36]	Adult and blood	2011	20

treatment with thionine for 4 weeks failed to give a positive clinical response to topical treatment in these patients.

There have been observations showing the relation between plasma selenium concentration acute-phase response marker in patients with different inflammatory disorders, including psoriasis, and malignancies [39, 40]. Ultraviolet B irradiation is a potent stimulant of TNF-α production and secretion by human keratinocytes in vitro. However, UVB can reach the upper dermis and suppress endothelial cells. Selenium compounds prevent in vitro the release of UV-induced proinflammatory cytokines (interleukin-6, interleukin-8, and TNF-α) by inhibition of mRNA for these cytokines in human keratinocytes [38, 41]. It also has been shown that preincubation of murine keratinocytes for 24 h with thionine or sodium selenite (thionine is more effective) results in inhibition of UV-induced interleukin-10 expression in these cells [37]. In contrast, a study found no significant changes in serum levels of interleukin-10 and TNF-α after three irradiations with narrow-band ultraviolet in five subjects with psoriasis [42]. Donadini et al. determined selenium levels in plasma and whole blood of 64 patients with psoriasis and in age-matched healthy controls and found no significant differences between these study groups [43].

British investigators found no differences in selenium absorption or atopic dermatitis and healthy controls, but the exchangeable total body selenium was lower in psoriasis patients than in controls [44]. Results of case–control studies proved that low selenium concentration can be a risk factor for some types of neoplasm and, thus, suggested that depressed selenium status also can be a risk factor for psoriasis, a disease characterized by cell hyperproliferation [45]. As it was mentioned above, experiments on selenium supplementation in psoriatic patients showed that selenium in inorganic forms, but not as thionine can achieve clinical improvement [17, 18].

Pastore et al. [45] investigated the immunological and redox markers in a group of psoriatic patients treated with efalizumab. They reported that the activities of GSH-Px and glutathione-*s*-transferase in granulocytes were remarkably increased, and catalase decreased exclusively in nonresponders vs complete or partial responders [46].

Role of Selenium Supplementation on Treatment of Psoriasis

As stated before, TNF-α is a cytokine important for inducing and maintaining psoriatic lesions. Serwin et al. [28] investigated the influence of selenium supplementation on soluble TNF-α receptor type 1 and topical treatment in psoriasis patients. They found that 4-week supplementation with thionine was ineffective in the acceleration of remission of psoriatic lesions (Table 2).

Previous studies found no significant differences in selenium absorption or excretion between psoriasis patients and controls after intravenous and oral administrations of SeMet, but the total exchangeable body selenium was lower in psoriasis patients.

Serwin et al. [28] suggested that insufficient dietary intake of selenium in a Polish population and in psoriasis patients, together with excessive desquamation or poor selenium absorption, may be additional reasons for low plasma selenium

Table 2 Effects of selenium supplementation on antioxidant status and apoptosis in patients with psoriasis

Selenium form	Subject and material	Value and effect	Reference
Sodium selenite	Adult and blood	Osteopontin and modulator	Kadry and Rashed [36]
Selenium	Adult and plasma Adult and erythrocytes	Erythrocytes-GSH-Px	Serwin et al. [3]
Sodium selenite	Adult and blood	GSH-Px and no effect P53, Fas, Bcl-2, Bax, oxidized guaninosine in skin biopsies, and no effects	Desilva et al. [35]
Ultraviolet B	Adult and serum		Serwin et al. [37]
Selenoprotein P	Adult and plasma Children and erythrocyte Adult and whole blood	Se-GSH-Px and no effect GSH-Px and no effect Se-GSH-Px and no effect	Serwin et al. [28]
Selenomethionine	Adult and serum Adult and whole blood	TNF-α and no effect sTNF-R1 and CRP	Serwin et al. [34]
Selenium-enriched yeast	Adult and blood	GSH-Px/lesions and no effect	Fairris et al. [47]
Selenium	Adult and plasma Adult and whole blood	Selenium levels and no difference between patients and control	
Selenium		Selenium levels and no difference between patients and control	

GSH-Px glutathione peroxidase, *GR* glutathione reductases, *Se* selenium

concentration. Supplementation with thionin in a Finnish patient with high baseline serum selenium concentration resulted in a significant increase in the number of CD4+ T cells and in nonsignificant increases in CD11c+ and CD1+ cells within the reticular dermis of psoriatic lesions [28].

In a study by Fairris et al. [47], 69 patients were supplemented daily with either 600 μg of selenium-enriched yeast, 600 μg of selenium-enriched yeast plus 600 IU of vitamin E, or placebo for 12 weeks. They found that neither supplementation regimen reduced the severity of psoriasis or produced side effects [47].

Desilva et al. [34] investigated the effects of oral selenium (400 μg) on expression of phosphorylated p53, Fas, Bcl-2, Bax, and oxidized guanosine and Langerhans and sunburn cells counts. They found that oral administration of sodium selenite did not significantly protect human skin against changes in marker proteins associated with ultraviolet-induced damage during TL01 phototherapy [34].

Kharaeva et al. [48] demonstrated for the first time that the combination of conventional therapy and supplementation with vitamin E, coenzyme Q10, and selenium resulted in an improvement in the clinical condition of patients with severe psoriasis as well as a reduction in oxidative stress. Supplementation using inorganic forms of selenium (sodium selenite and selenate) is also reported to lead to clinical improvement in patients with psoriasis [28, 47].

Future Directions

There are two main future directions: (1) selenium is an essential trace element with immune-modulating and antiproliferative properties, with an influence over the immune response either through a change in the expression of cytokines and respective receptors or by making immune cells more resistant to oxidative stress. Information on selenium in psoriasis is scarce. The data presented in the current study indicate that patients with psoriasis have low concentrations of selenium. In addition, reports are conflicting on relationships between psoriasis and blood and tissue selenium levels and GSH-Px activity in human and animals (Table 1). Hence, further experiments are needed to elucidate the effects of selenium supplementation in psoriasis. (2) Inflammation induces oxidative stress, and psoriasis is also an inflammatory diseases. Hence, supplementation with organoselenium compounds, such as thionin and selenocystein, may be useful for the treatment of psoriasis through inhibition of oxidative stress and inflammation. These alternatives should also be clarified by future experiments.

Acknowledgments There is no financial support in the current study.

Conflict of Interest None.

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