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Invited review

Sodium selenite and cancer related lymphedema: Biological and pharmacological effects

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ABSTRACT

A significant percentage of cancer patients develop secondary lymphedema after surgery or radiotherapy. The preferred treatment of secondary lymphedema is complex physical therapy. Pharmacotherapy, for example with diuretics, has received little attention, because they were not effective and only offered short-term solutions. Sodium selenite showed promise as a cost-effective, nontoxic anti-inflammatory agent. Treatment with sodium selenite lowers reactive oxygen species (ROS) production, causes a spontaneous reduction in lymphedema volume, increases the efficacy of physical therapy for lymphedema, and reduces the incidence of erysipelas infections in patients with chronic lymphedema. Besides biological effects in reducing excessive production of ROS, sodium selenite also displays various pharmacological effects. So far the exact mechanisms of these pharmacological effects are mostly unknown, but probably include inhibition of adhesion protein expression.

Contents

1. Introduction

Secondary lymphedema is a common side effect of cancer treatment. The incidence rate varies greatly because of the absence of uniform measurement, definition and reporting [1]. Most data is available for breast cancer survivors. The incidence rates range between 13% to 65% [1]. Secondary lymphedema occur after lymph node resection. Lymph drainage routes can be damaged, which causes accumulation of lymph fluid in the interstitial tissue of related limbs. The subsequent tissue swelling can cause pain, discomfort, heaviness, distortion, and reduced mobility and function [2]. Both physical and mental quality of life is affected [3].

Currently, there is no curative therapy available. It can only be managed. The goal is to decrease limb size and maintain it, prevent complications, improve limb function, and overall well being [4]. The most important treatment is complex physical therapy, which includes complete decongestive therapy. It also consists of manual lymph drainage, exercise, nonelastic wrapping, use of compression garments, and skin care [1]. A second therapy option is low-level laser therapy, which can effectively reduce limb volume, extracellular fluid, and tissue hardness in one third of breast cancer patients [5,6]. Pharmacotherapy has received little attention, prob-

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ably because many drugs were not effective and only very few offer long-term solutions [1].

Paskett et al. mentioned only one drug, sodium selenite, in a review regarding cancer-related lymphedema [1]. The authors concluded, that sodium selenite shows promise as a cost-effective, nontoxic anti-inflammatory agent [1]. The Cochrane analysis on selenium in cancer patients from 2006 included two trials from Kasseroller et al. and Zimmermann et al. [7,8]. The authors concluded, that sodium selenite might reduce the incidence of recurrent erysipelas infections after breast cancer treatment, but the results should be interpreted with caution and should not be generalized to other populations [9].

This review summarizes the current literature regarding sodium selenite in lymphedema treatment with emphasis on probable mode of action of sodium selenite.

1.1. Lymphedema

The Iowa women's health study provided new data regarding lymphedema in breast cancer survivors [3]. The study included 1,287 women with unilateral breast cancer. 8.1% were diagnosed with lymphedema. Further 37.2% women reported arm symptoms without diagnosed lymphedema. After multivariate adjustment, both women with diagnosed lymphedema and women with arm symptoms had lower physical and mental health related quality of life (HRQOL) (Medical Outcomes Study Short Form-36). Only half of the women with diagnosed lymphedema received treatment (51.5%). Furthermore, only 39.8% of the women with arm symptoms ever heard of lymphedema. This lack of knowledge about lymphedema may prevent woman with arm symptoms from seeking evaluation or treatment as only 10.3% talked to their practitioner about the different appearance of one arm and only 1.7% received treatment [3].

A 5-year, population-based prospective study (n = 6,319) evaluated the incidence, degree, time course, treatment, and symptoms of lymphedema in breast cancer patients after tumor resection [10]. The five-year cumulative incidence of lymphedema was 42 (42%) per 100 women. Incidence was higher for woman <50 years (50%) compared to woman >80 years (26%). In the first three years 23% reported no more than mild lymphedema, 12% reported moderate or severe lymphedema, and 2% reported a chronically moderate or severe form. 47.3% of the women with lymphedema received at least one type of treatment. Women with moderate or severe lymphedema were more likely to be treated (68% vs. 37%). Mostly exercise, sleeve, elevation, or massage was used for therapy. The study also showed, that symptoms before the first occurrence of lymphedema, for example jewelry too tight or clothing too tight, were associated with higher probability of later lymphedema (Hazard Ratio (HR) 7.37; 95% CI, 4.26–12.76, respectively HR 5.47; 95% CI 1.98–15.10). Till now, there was no investigation, if a prompt treatment of those early symptoms can prevent lymphedema or progression from mild to moderate or severe form.

The incidence rate is much higher after the resection of head and neck tumors. Three-quarter of the patients have some form of late-effect lymphedema [11]. Most patients displayed a combination of external and internal lymphedema (50.8%). External lymphedema stage I affected 18.5% of the patients, and 27.2% displayed stage II lymphedema. Internal lymphedema were graded as moderate in 45.5% and as severe in 20% of the cases.

1.2. Selenium status of patients with lymphedema

Selenium status of patients with lymphedema and/or lipedema was determined in a new study. Selenium concentration in whole blood was measured in 234 patients, which were treated for lymphedema in a specialist clinic in Germany (Lympho-Opt Clinic Pommelsbrunn-Hohenstadt, Germany). Selenium measurement was performed using microwave digestion and flameless atomic absorption spectrometry in a certified laboratory (biosyn Arzneimittel GmbH, Fellbach, Germany).

Table 1
Selenium status in lymphedema and/or lipedema patients in Germany. Mean value ± standard deviation.

Subgroups	patient number	whole blood selenium concentration [μg/l]
overall	234	102.4 ± 19.8
lipedema	101	99.4 ± 18.0
lymphedema	160	103.8 ± 21.6
lymphostatic elephantiasis	14	87.5 ± 18.3
primary lymphedema	32	114.2 ± 27.2
secondary lymphedema	60	102.7 ± 19.8
lymphedema stage I	9	109.1 ± 17.9
lymphedema stage II	80	106.5 ± 23.9
lymphedema stage III	27	91.5 ± 14.4
cancer-related lymphedema	31	106.5 ± 19.4
mamma carcinoma + lymphedema	11	107.6 ± 15.4
diabetes + lymphedema	9	95.2 ± 15.5
hypothyroidism + lymphedema	20	103.6 ± 14.5
obese + lymphedema	92	100.0 ± 19.6
morbidly obese + lymphedema	24	94.7 ± 15.5

The mean selenium concentration was 102.4 ± 19.8 μg/l. The German authorities defined a selenium deficit as values below 100 μg/l selenium in whole blood [12]. Using this parameter 44% of the patients exhibited a selenium deficit. Significantly more patients with lymphedema stage III displayed reduced selenium levels (78% vs. 44%; p = 0.001).

The comparison of selenium values in lymphedema and lipedema showed no significant difference (103.8 ± 21.6 μg/l vs. 99.4 ± 18.0 μg/l) (Table 1). But patients with lymphostatic elephantiasis (stage three lymphedema and/or lipedema) displayed the lowest selenium values (87.5 ± 18.3 g/l; p = 0.014). Selenium concentration was higher in primary lymphedema (114.2 ± 27.2 μg/l vs. 103.8 ± 21.6 μg/l; p = 0.0312). There was also a strong trend regarding a significant difference between primary and secondary lymphedema (114.2 ± 27.2 μg/l vs. 102.7 ± 19.4 μg/l; p = 0.056) (Fig. 1).

Furthermore, selenium status declined with increasing lymphedema stage. Selenium concentration was significantly reduced in lymphedema stage III compared to stage I and II (91.5 ± 14.4 μg/l; p = 0.0109 respectively p = 0.0002) (Fig. 2).

Patients with cancer related lymphedema showed no significantly reduced selenium status compared to other patients with secondary lymphedema (106.5 ± 19.4 μg/l vs. 102.7 ± 19.8; p = 0.4717). 39% of the lymphedema and/or lipedema patients were obese. While selenium level was not significantly different in obese patients, morbidly obese patients displayed significantly reduced whole blood selenium concentration compared to all patients (103.8 ± 21.6 μg/l vs. 94.7 ± 15.5; p = 0.0398).

Surprisingly, selenium status was higher in patients with primary lymphedema compared to patients with secondary lymphedema. While the underlying causes are different for primary and secondary lymphedema, the consequences, which result in the development of lymphedema, are similar. At the moment, there is no explanation for higher selenium status in primary lymphedema, especially as patients with lymphostatic elephantiasis, regardless of lymphedema type, displayed the lowest mean selenium values.

In women BMI ≥ 30 kg/m^2 is significantly associated with reduced selenium status (p = 0.01) [13]. Morbidly obese patients (BMI ≥ 40 kg/m^2) display significantly reduced serum selenium concentration (86.08 μg/l vs. 101.14 μg/l; p < 0.0001) [14]. Significantly reduced selenium status in morbidly obese patients is probably due to obesity related oxidative stress [15]. Also, obe-

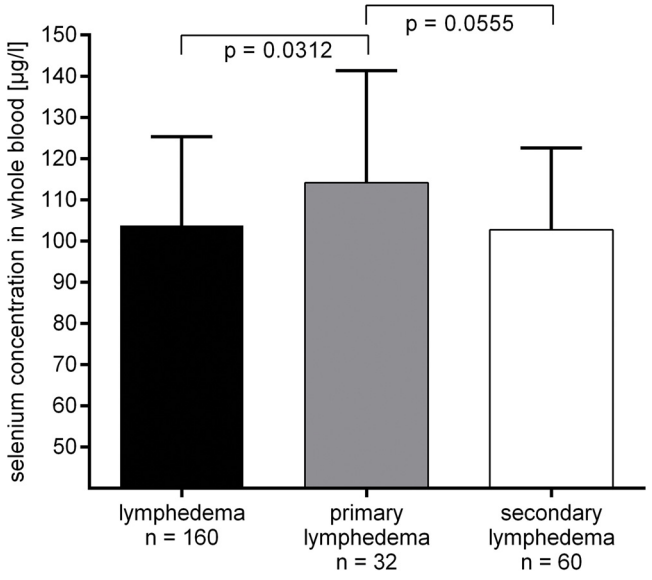

Fig. 1. Selenium concentration in whole blood was significantly increased in primary lymphedema. The comparison between primary and secondary lymphedema displayed a strong trend for reduced selenium status in secondary lymphedema. Statistical significance was calculated using the non-parametric Mann-Whitney *U* test; p-values < 0.05 were considered statistically significant. Data were analyzed and figures were created using GraphPadPrism 6 (GraphPad Software, Inc., La Jolla, CA, USA).

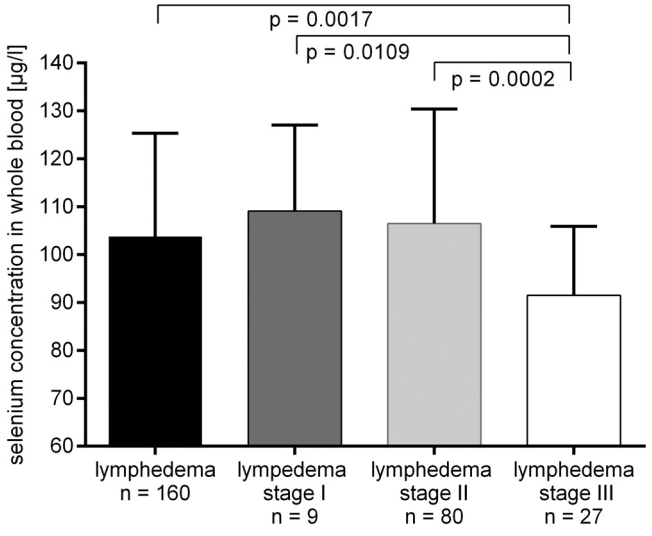

Fig. 2. Selenium concentration in whole blood decreased with increasing lymphedema stage. Statistical significance was calculated using the non-parametric Mann-Whitney *U* test; p-values < 0.05 were considered statistically significant. Data were analyzed and figures were created using GraphPadPrism 6 (GraphPad Software, Inc., La Jolla, CA, USA).

sity is associated with a state of chronic inflammation, which also contributes toward a pro-oxidant environment in obesity [16].

The study showed that patients with severe lymphedema were significantly more often affected by reduced selenium levels. Those results strongly indicate an increased selenium requirement in these patients. The cause for increased selenium requirement could be enhanced oxidative stress and an elevated inflammatory activity. Siems et al. determined, that in the tissue of chronic lymphedema the formation of reactive oxygen species (ROS) was enhanced and lipid peroxidation processes were accelerated [17].

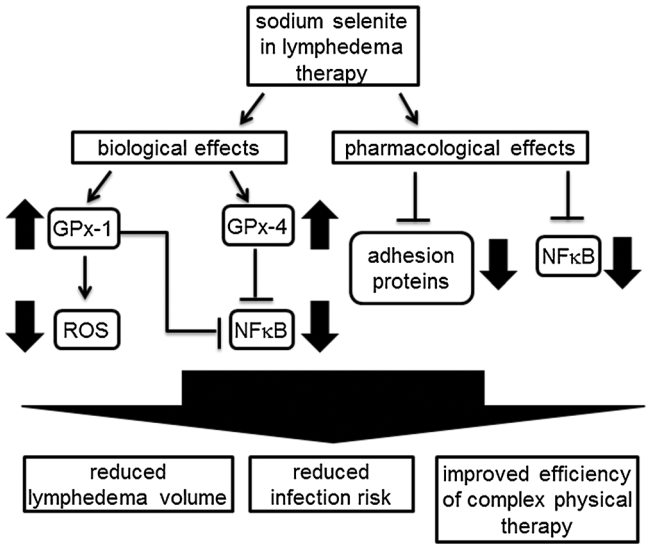

Fig. 3. Sodium selenite reduced lymphedema volume and improved efficiency of complex physical therapy [19]. GPx–1 = glutathione peroxidase 1; GPx–4 = glutathione peroxidase-4.

1.3. Sodium selenite treatment for secondary lymphedema

As Micke et al. stated, selenium has a proven antiedematous effect, which is neither widely published nor accepted [18]. Several trials with oral sodium selenite treatment showed, that sodium selenite lowers ROS production, causes a spontaneous reduction in lymphedema volume, increases the efficacy of physical therapy for lymphedema, and reduces the incidence of erysipelas infections in patients with chronic lymphedema [18]. The results of these trials are summarized below (Table 2).

Kasseroller et al. evaluated the effect of oral sodium selenite in combination with combined physical decongestive therapy in 179 lymphedema patients [19]. The intervention period was three weeks. In the first week daily sodium selenite treatment was 1,000 µg selenium. In the second and third week 300 µg selenium per day were supplemented. Follow-up period was three months. During this period patients received 100 µg selenium per day. The lymphedema volume was significantly more reduced in the intervention group compared to combined physical decongestive therapy alone (- 52.0 ± 18.0% vs. 43.0% ± 16.0%; $p < 0.01$) [19]. Also the skin fold index and mobility were significantly more improved with sodium selenite treatment ($p < 0.05$ respectively $p < 0.001$) [19]. In the sodium selenite supplemented group the erysipelas incidence was 0% compared with 50% in the placebo group [19].

Micke et al. determined the effect of oral sodium selenite in radiation-associated secondary lymphedema [20]. In this exploratory study 48 patients were treated with up to 500 µg selenium per day for 4–6 weeks. Twelve patients displayed lymphedema of the arm and 36 patients lymphedema of the head and neck region. More than three-quarter of the patients showed an improvement of one stage or more according to the Földi and Miller score [20]. 65% of patients with interstitial grade III or IV endolaryngeal lymphedema displayed a substantial reduction in endolaryngeal swelling [20]. Therefore, no tracheotomy was necessary in these patients.

These results were confirmed in a double-blind, randomized, prospective study [8]. Zimmermann et al. treated 20 patients with oral surgery intravenously with 1,000 µg selenium in form of sodium selenite pre-, intra- and post operation. From day 1–21 sodium selenite dosage was 1,000 µg selenium per day intravenously or orally. The lymphedema volume reduced significantly after one week in the sodium selenite supplemented group (-

Table 2
Lymphedema trials with sodium selenite.

trial	intervention	results
Kasseroller et al. [19]		
placebo-controlled, double blind	selenium as sodium selenite	Increased whole blood selenium concentration after 3
N = 179	Week 1:	weeks (112 ± 24 μg/l; p < 0.001)
intervention group n = 90	1,000 μg per day	Reduced lymphedema volume compared to placebo group
placebo group n = 89	Week 2 + 3:	(p < 0.01)
Breast cancer patients	300 μg per day	Improved skin fold index and mobility (p < 0.05 and
baseline whole blood concentration	Follow-up period (3 month):	p < 0.001)
69 ± 8 μg/l	100 μg per day	Reduced erysipelas incidence (0% vs. 50%)
Micke et al. [20]		
N = 48	selenium as sodium selenite	Lymphedema improvement of one stage or more (Földi
Breast cancer (n = 12)	4–6 weeks:	and Miller score)
head and neck cancer (n = 36)	500 μg per day	Reduction in endolaryngeal swelling
Zimmermann et al. [8]		
Prospective, randomized, placebo-controlled,	selenium as sodium selenite	Increased whole blood selenium concentration after
double-blind	1,000 μg pre, intra, and post operation	operation, week 1 and week 2 (p = 0.001, p = 0.002,
N = 20	1,000 μg for 21 days	p = 0.000)
intervention group n = 10		Reduced lymphedema volume compared to placebo group
placebo group n = 10		(p = 0.009)
squamous cell carcinoma of the head and neck		

6%; p = 0.009). The severity of the lymphedema was negatively correlated with blood selenium concentration and glutathione peroxidase activity. Also ROS concentration was positively correlated with the extent of lymphedema.

1.4. Biological effect of sodium selenite treatment

In lymphedema tissue oxygen supply is restricted, giving rise to the excessive production of ROS [21]. The excessive amount of ROS induces an inflammatory reaction and affected lymph vessels are invaded by phagocytes and other activated leucocytes. The ensuing respiratory burst triggers a cascade of peroxidative reactions, which results in the formation of 4-hydroxynonenal (4-HNE) and malondialdehyde (MDA) as measured in erythrocytes and blood serum [19]. Those metabolites display proinflammatory [22], vasoconstrictive [23], cytotoxic [24] and potential carcinogenic [25] properties. To detoxify those metabolites high amounts of glutathione (GSH) are used and oxidized (GSSG). Siems et al. showed that GSH concentration in blood was decreased in chronic lymphedema patients and GSSG was elevated, resulting in a threefold higher glutathione ratio, an indicator for oxidative stress [17].

The concentration of lipid peroxidation products MDA and 4-HNE increased threefold in the serum of lymphedema patients, respectively twofold [17]. Lymphedema patients treated with oral sodium selenite displayed a rapid increase in GSH and a slower decrease in GSSG as well as 4-HNE measured in erythrocytes, respectively blood serum [26]. Selenium as part of selenoproteins thioredoxin reductase and glutathione peroxidase is essential for redox reactions. Therefore sodium selenite supplementation probably increased activity of these selenoproteins elevating GSH concentration and decreasing GSSG level. The increased GSH concentration could also reverse the effect of GSH depletion, which impedes the function of glutathione peroxidase.

One of the most important intracellular antioxidant enzymes is the selenoprotein glutathione peroxidase. The crucial factor for biosynthesis of glutathione peroxidase is availability of selenium. High dose sodium selenite increased glutathione peroxidase activity noticeably at day three in sepsis patients [27]. Selenium deficiency significantly reduces liver glutathione peroxidase-1 activity, the most common selenoprotein [28]. Another selenoprotein, thioredoxin reductase, is also capable to degrade hydroperoxide [29]. Selenoproteins with extracellular antioxidant functions are glutathione peroxidase 3 and selenoprotein P, whereby selenoprotein P is also the transport protein for selenium [29].

A functional gene expression analysis of a mouse model of acute, acquired lymphedema showed that whole panels of genes involved in the immune response, stress response, and complement activation were induced in lymphedema tissue [30]. These included several selenoproteins. The fold-change was highest for selenoprotein P (2.8:1), selenoprotein W (2.2:1), and glutathione peroxidase 1 (1.9:1). Also selenoprotein K was upregulated. These results confirmed the important role of selenoproteins in lymphedema. Most of the upregulated selenoproteins are so-called stress-responsive selenoproteins. They are highly dependent on an adequate selenium supply. Even marginal selenium deficiency prevents maximal activity for example for glutathione peroxide 1, which requires selenium concentration of 95 μg/l in blood plasma [31]. In the trial by Hurst et al. optimal concentration of selenoprotein P was reached at 124 μg/l selenium in plasma [32].

Besides their antioxidant capacity selenoproteins also play a major role in the immune system. Adequate selenium status is important for initiating immunity. But selenoproteins are also involved in regulating excessive immune response and chronic inflammation [33]. Selenium deficiency has been recognized to negatively impact immune cells during activation, differentiation, and proliferation [33]. Besides those effects based on increased oxidative stress, selenoproteins are linked to protein folding and calcium flux [33]. Huang et al. provided an in depth review about the role of selenoproteins in inflammation and immunity [33].

In summary, not only an adequate selenium supply is necessary to decrease excessive ROS production in lymphedema, but the selenium requirement is probably higher compared to healthy people.

1.5. Pharmacological effect of sodium selenite treatment

The first evidence, that sodium selenite has beneficial effects in chronic lymphedema were noted in 1991 [19]. A patient with acutely inflamed lymphedema of the arm was treated with 800 μg selenium in form of sodium selenite orally. Ten to fifteen minutes after the supplementation the inflammation and edema were visibly reduced [19]. This fast reaction can not be explained with sole biological effects of sodium selenite. Therefore, sodium selenite probably also displays direct pharmacological effects in lymphedema tissue.

Deranged immune traffic plays a role in the pathogenesis of lymphedema [30]. In normal immune traffic, mononuclear phagocytes and lymphocytes enter the afferent lymph vessels and the lymph nodes to elicit primary immune response before reentering the vasculature [34]. In chronic lymphedema, the impairment of lymphocytes trafficking from skin to regional lymph nodes leads to inefficient clearance of foreign antigens, which provides the substrate for chronic inflammatory changes [30].

In 2000, Kasseroller et al. postulated a hypothesis how sodium selenite exerts pharmacological effects in lymphedema [19]. They proposed that sodium selenite inhibits the expression of adhesion proteins. The excessive amount of ROS induces an inflammatory reaction and affected lymph vessels are invaded by phagocytes and other activated leucocytes. Adhesion molecules on the surface of immune cells attach to the walls of lymph capillaries [19]. As a result venous lymphatic insufficiency increases further. Inhibition of adhesion proteins reduces the ability of immune cells to attach to lymph capillaries. Venous lymphatic insufficiency is decreased and the efficiency of complex physical therapy is improved (Fig. 3) [19].

In 2012, Huang et al. showed that for leucocytes to migrate into inflammatory tissue an efficient adhesion is required [33]. Therefore, monocytes and leucocytes express endothelial adhesion molecules. Sodium selenite supplementation (2 μg/ml selenium as sodium selenite for 16 h) induced metalloproteinase-dependent L-selectin, which resulted in decreased monocyte rolling and adhesion [35]. These effects were reversible using broad-range matrix metalloproteinase inhibitor GM6001. Also, several studies showed that sodium selenite (100 nmol/l selenium as sodium selenite for 48 h or 0–2 μM sodium selenite for 24 h) inhibited expression of vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), E-selectin and P-selectin [36–38]. This new data supports the hypothesis of Kasseroller et al. [19].

Sodium selenite also inhibited nuclear factor-κB (NFκB) directly through adduct formation with the essential thiols of this transcription factor in human T cells and lung adenocarcinoma cells [39]. The inhibition was dose-dependent. Complete NFκB inhibition was reached at 7 μM sodium selenite. NFκB is required for transcription of above mentioned adhesion proteins. Also, glutathione peroxidase 1 and 4 inhibited NFκB activation [40,41]. The inhibitory effect of sodium selenite on NFκB depends on both, biological and pharmacological, effects. NFκB also plays a major role in inflammation. Pro-inflammatory cytokines activate NFκB and NFκB induces the expression of cytokines, chemokines, and adhesion molecules [42]. The inhibition of NFκB by sodium selenite is probably one reason for the anti-inflammatory effect of sodium selenite in lymphedema.

1.6. Prospective trials

There are several questions the previous trials did not answer. First of all, the patients were treated with sodium selenite only for a few weeks. But both, primary and secondary lymphedema, are lifelong conditions. Therefore, future trials should be designed to answer the question: How long should treatment last? The duration of trials in other indications such as during radiotherapy or in sepsis patients, which also used high dose sodium selenite, was also only weeks [27,43]. In these trials high dose sodium selenite displayed no relevant side effects. A recent trial determined the maximum tolerable dose of sodium selenite in cancer patients [44]. The results showed that the patients displayed hardly any symptoms at dose levels below 3,000 μg/m^2. At dose level 3,000 μg/m^2 and above 15% of the patients had garlic smell of breath. At dose level 4,500 μg/m^2 the most common side effects were nausea, vomiting, and fatigue. Those were reversible within one or two days. Chinese studies showed that only long term intake at or above 910 μg per day resulted in selenosis symptoms [45].

Another question concerns the measurement of selenium level. In lymphedema trials patients displayed low blood selenium level [7,8]. Those patients benefited from sodium selenite treatment. Selenium measurement before therapy start and during therapy should be useful to determine the adequate selenium dose. Future trials should establish parameters, which selenium dose would be sufficient to increase selenium status to an adequate level. So far there is no uniform definition of selenium deficiency. There are diseases associated with selenium deficiency: Kashin-Beck and Keshan disease. These selenium deficiency diseases mostly occurred at a mean value of 21 μg/l selenium in serum [46]. But all-cause mortality was increased for serum selenium concentrations below 106 μg/l [47].

Also the parameter for measurement is important: whole blood or plasma/serum concentrations. Selenium serum concentration reflects short term status. Whole blood selenium also takes into account erythrocyte selenium and reflects long-term status due to the incorporation of selenium during protein synthesis in cells [48,49]. Hence, whole blood selenium allows a better assessment of selenium status.

2. Conclusions

The preferred treatment of secondary lymphedema is complex physical therapy. Pharmacotherapy has received little attention, but sodium selenite showed good results in reduction of lymphedema volume, increasing the efficacy of complex physical therapy, and in incidence reduction of erysipelas infections in patients with cancer-related lymphedema. Besides biological effects in reducing excessive production of ROS, sodium selenite also displayed various pharmacological effects. Sodium selenite can directly inhibit the expression of adhesion proteins and NFκB. The positive effect of sodium selenite on infection risk probably depends on both, biological and pharmacological, effects. Further trials are needed to confirm these results and to specify selenium dosage and therapy duration.

Conflict of interest

Christina Pfister and Horst Dawzcynski are employed by biosyn Arzneimittel GmbH. Selenium measurements detailed under "Selenium status of patients with lymphedema" were performed by biosyn Arzneimittel GmbH. Franz-Josef Schingale did not receive any direct financial support or funding.

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