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Invited review

Sodium selenite and cancer related lymphedema: Biological and pharmacological effects

Christina Pfister[a,*], Horst Dawzcynski[b], Franz-Josef Schingale[c]

[a] biosyn Arzneimittel GmbH, Schorndorfer Straße 32, 70734 Fellbach, Germany
[b] biosyn Arzneimittel GmbH, Schorndorfer Straße 32, 70734 Fellbach, Germany
[c] Lympho Opt Fachklinik, Happurger Str. 15, 91224 Hohenstadt, Germany

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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.

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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-

* Corresponding author.
E-mail address: chpfister@t-online.de (C. Pfister).

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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-