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Would selenium supplementation aid in therapy for Chagas Disease?

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Abstract

Chagas disease, a neglected tropical disease discovered over 100 years ago, is caused by the intracellular parasite *Trypanosoma cruzi* and is most frequently associated with chronic cardiomyopathy and digestive disorders. Initial invasion of cells is followed by progressive inflammatory destruction of heart, muscles, nerves, and gastrointestinal (GI) tract tissue. About 30% of patients progress to a chronic cardiomyopathy associated with increased morbidity and mortality. Seven to 10% of patients develop megasyndromes involving the GI tract, in particular, the esophagus and the colon. Results from several studies suggest that selenium (Se) deficiency may be an important factor in the pathogenesis of Chagas disease. In this opinion article, Se supplementation is proposed as an adjuvant therapy for treatment of chronic Chagas disease.

The need for new therapeutic regimens

Despite efforts over the century since its discovery, Chagas disease, caused by the protozoan, *Trypanosoma cruzi*, remains a health problem in Latin America. Treatment of Chagas disease requires two approaches: (i) treatment of acute infection aimed at killing the parasite and (ii) treatment aimed at minimizing the pathological effects that remain even after reduction of the parasite load. The anti-trypanosomal agents, benznidazole and nifurtimox, are effective against *T. cruzi* during the acute infection, however, they have undesirable side effects and their effectiveness for use in chronic patients is still controversial. These drugs were developed over forty years ago [1]. Recently an antifungal, posaconazole, was used to treat reactivation of *T. cruzi* in a patient with promising results [2]. However, the cost of production of posaconazole may prohibit its widespread use [3].

One third of chronic chagasic patients develop symptoms, with cardiomyopathy being the most common. Chronic chagasic cardiomyopathy (CCC) is a progressively debilitating disease. Heart transplant is the only currently available treatment in severe cases, although

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tissue engineering and cell therapy continue to be investigated as treatments to recover heart function [4]. There are also limited treatment options for the digestive syndrome which includes megasyndromes of the GI tract. For example, surgical treatment is often the only option to alleviate symptoms of chagasic megacolon and megaesophagus [5]. Thus, the need for alternative therapies is essential and continues to be explored.

Antioxidant Therapy

Recent studies have addressed the oxidative status and antioxidant defense capabilities during the course of infection and progression of chagasic disease in human patients and experimental models [6–11]. Oxidative stress can be caused by the inflammatory processes occurring during infection with *T. cruzi* and also by the drug therapy itself. In chronic chagasic patients a combination of antioxidant supplementation consisting of vitamin E and vitamin C was shown to attenuate oxidative insult (as evidenced by reduced lipid peroxidation and protein carbonyl contents) [7]. Vitamin E supplementation also attenuated the oxidative insult promoted by benznidazole therapy [2]. In these studies the effects of supplementation were most beneficial to patients before advancement to congestive heart failure.

Selenium

Selenium (Se) is a trace element essential to organisms from bacteria to humans. It plays a role as an antioxidant at the cellular level, providing protection against free radical damage and oxidative stress. In mammals, one of the best characterized roles of Se is its incorporation in the active site of different isoforms of glutathione peroxidase, an enzyme that protects polyunsaturated lipids in biological membranes [12]. At low doses, Se supplementation has been shown to contribute to the antioxidant response in rats infected with *Trichinella spiralis* [13]. Se plays a role in the immune system [14] and was shown to potentiate vaccine induced immunity to malaria in mice [15]. In mice, Se supplementation has also been found to enhance the protective response to *Toxocara canis* larvae [16], decrease coxsackie virus induced heart disease [17,18], exhibit a protective effect against infection with murine leukemia virus [19], inhibit infection with *Cryptosporidium parvum* [20], and provide protection against H1N1 influenza virus infection [21]. Se deficiency has been associated with both an altered immune response and increased lung pathology in mice infected with different influenza virus strains [22,23], extensive cardiac pathology in mice infected with a benign amyocarditic coxsackievirus B3 [24], decreased immune response and higher susceptibility of mice to *C. parvum* infection [25], and an altered innate immune response to *Listeria monocytogenes* infection in mice [26]. It is also interesting to note that in some cases the altered immune response in Se deficient mice can be beneficial. For example, Se-deficient mice were protected from virus-induced mortality when they were infected with a virulent influenza strain (A/Puerto Rico/8/34) [22]. Furthermore, it was shown that increased dietary supplementation with vitamin E and Se led to increased tissue cyst number, tissue pathology, and weight loss in mice during infection with *Toxoplasma gondii* [27]. Thus, Se supplementation or depletion may prove to be beneficial depending on the particular infectious agent and state of the host.

Selenium: an adjuvant therapy in Chagas Disease?

In 2002, a study of advanced chronic chagasic patients reported that low Se levels were positively correlated with cardiac insufficiency [28]. Although Se deficiency can occur in areas where the soil content of Se is low, the patients in the study all lived in geographic areas with adequate soil Se content. Experiments designed to investigate the role of Se demonstrated an increased susceptibility to infection in mice fed Se deficient chow [29] and increased severity of myopathy was observed in Se depleted chronically infected mice [30].

Se supplementation alleviated heart muscle damage [31] and had previously been shown to reduce parasitemia and mortality in infected mice [32]. Se intake has been associated with prevention of Keshan disease and other cardiac conditions [17,18,33–37].

Recently, studies were reported designed to evaluate the effect of Se supplementation on the development of chronic cardiomyopathy in *T. cruzi* infected mice [38]. It had previously been shown that right ventricular dilatation is a marker for severity of the cardiac disease in infected mice [39]. Se supplementation (2 ppm Se supplied as sodium selenate in the drinking water) beginning two weeks prior to infection of mice with *T. cruzi* prevented the extreme dilation of the right ventricle which has been routinely observed in chronically infected mice while Se supplementation of uninfected mice had no effect on cardiac dimensions [38]. Furthermore, Se supplementation initiated during the chronic stage of infection was able to reverse ECG abnormalities and inflammation in the pericardium close to the atrioventricular node [38]

In another recent study the effect of Se supplementation on the gastrointestinal manifestations of mice chronically infected with *T. cruzi* was evaluated [40]. In chronically infected mice enlargement of the intestine associated with decreased intestinal motility was observed. Se supplementation (as 2 ppm Se supplied as sodium selenate in the drinking water or as 3 ppm Se in the chow as Se-methylselenocysteine) beginning two weeks prior to infection reduced intestinal dilation and preserved intestinal motility. Since this study focused on preventing intestinal alterations, further studies are required to demonstrate a protective effect of Se on pre-existing intestinal disturbances. In our studies of the heart and GI tract in *T. cruzi*-infected CD1 mice, Se supplementation had no effect on parasitemia, thus, Se may act through modulation of the inflammatory, immunological, and/or antioxidant responses to *T. cruzi* infection. Table 1 summarizes the results of studies of Se-supplemented or Se-deficient animals infected with various pathogens.

The recommended dosage for Se supplementation is 100 µg since Se can be dangerously toxic in higher doses. Symptoms of Se-poisoning include neurological damage, skin lesions, loss of hair, cirrhosis of the liver, pulmonary edema, and death. According to the Institute of Medicine Food and Nutrition Board the recommended daily adequate intake of Se for both men and women is 55 µg/day with a tolerable upper intake level of 400 µg/day for adults [41]. A daily dosage of 100 µg has been shown to revert arrhythmias and cardiomegaly and lead to an increase in left ventricle ejection fraction in patients with severe disabilities under long-term tube feeding [34]. Thus, the use of Se supplementation in chagasic patients before the development of heart failure is proposed to provide a beneficial effect in preserving heart function. A phase III clinical trial was designed and is under way to test the hypothesis that Se treatment in chronic chagasic patients can reduce the rate of progression of slight and moderate heart dysfunction (www.clinicaltrials.gov; identifier: NCT00875173: Selenium treatment and Chagas cardiopathy). The primary endpoint is a reduction of 50% in the rate of progression of heart dysfunction after 5 years, as assayed by the frequency of cases with no or minimal decrease of left ventricular ejection fraction assessed by echocardiography. If the benefit of Se treatment in chagasic patients is confirmed, a strategy using an adequate concentration as a treatment in the daily diet could revolutionize the therapeutic regimen for Chagas disease cardiomyopathy. It would be expected that Se supplementation would impede the progression of left ventricular dysfunction in patients with mild heart disease and would improve cardiac function in patients with moderate heart disease.

Concluding Remarks

The progression of cardiac disease observed in the experimental mouse model may be analogous to the slow changes that occur during the early chronic phase of *T. cruzi* infection

in humans; therefore, Se supplementation might be useful for halting disease progression in patients at this stage of infection. Se supplementation, in combination with specific anti-trypansomal agents and/or other anti-oxidants, may provide a superior therapeutic protocol to modulate the inflammatory, immunological, and antioxidant responses involved in intestinal and cardiac disturbances caused by *T. cruzi* infection.

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Table 1

Summary of studies of Se-supplemented or Se-deficient animals infected with various pathogens

Selenium Supplemented				
Pathogen	Animal	Form of Supplement	Effect	Refs.
<i>Trichinella spiralis</i>	Rat	Sel-plex (organic, Alltech) (0.5 mg/kg)	⁺ ^a	[13]
<i>Plasmodium berghei</i>	Mice	sodium selenite (2.5 ug Se/ml, orally)	+	[15]
<i>Toxocara canis</i>	Mice	sodium selenite (0.06 µg ip or orally)	+	[16]
<i>Coxsackie virus during murine AIDS</i>	Mice	sodium selenite (0.833 mg in chow)	+	[17]
<i>Coxsackie virus</i>	Mice	sodium selenite (5 ppm, orally)	+	[18]
<i>Murine leukemia (MuLV)</i>	Mice	sodium selenite (0.1 mg/kg ip or orally).	+	[19]
<i>Cryptosporidium parvum</i>	Mice	sodium selenite (12 µM, orally)	+	[20]
<i>Influenza (H1N1)</i>	Mice	sodium selenite (0.5 mg Se/kg in chow)	+	[21]
<i>Toxoplasma gondii</i>	Mice	8 ppm selenium in chow	⁻ ^b	[27]
<i>Trypanosoma cruzi</i>	Mice	sodium selenate (2 ppm, orally) Se-methylselenocysteine (organic, 3 ppm in chow)	⁺ ⁺	[31,32,38] [40]
Selenium Deficient				
Pathogen	Animal	Se Deficient Chow	Effect	Refs.
<i>Influenza (A/Puerto Rico/8/34)</i>	Mice	<2.7 µg Se/kg	+	[22]
<i>Influenza (A/Bangkok/1/79)</i>	Mice	<2.7 µg Se/kg	–	[23]
<i>Coxsackie virus</i>	Mice	<2.7 µg Se/kg	–	[24]
<i>Cryptosporidium parvum</i>	Mice	0.005 mg Se/kg	–	[25]
<i>Listeria monocytogenes</i>	Mice	0.005 mg Se/kg	–	[26]
<i>Trypanosoma cruzi</i>	Mice	0.005 mg Se/kg	–	[29,30]

^a
+ = beneficial effect^b
– = detrimental effect

Abbreviations: ip, intraperitoneal.