



REVIEW ARTICLE

Cardiomyopathy Secondary to Selenium Deficiency: A Review of Clinical Cases

Nigel Amankwah¹ and Zhiyong Han^{2,*}

¹*School of Medicine and Health Sciences, The George Washington University, Washington, DC, USA*

²*Department of Medical Sciences, Hackensack Meridian School of Medicine at Seton Hall University, Building 123, 340 Kingsland Street, Nutley, NJ 07110, USA*

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Abstract:

Background:

Selenium is an essential micronutrient for the human body because it is needed for the synthesis of selenoproteins, which have various biological functions. As a result, selenium deficiency associated with diets and/or environments manifests in different disease states such as epilepsy, multimicore disease and cardiovascular injury which in some cases is a presage of cardiomyopathy.

Objective:

This objective was to review published cases and identify selenium-responsive cardiomyopathy due to selenium deficiency by various factors.

Methods:

Published case reports in English were identified and extracted from PubMed, Scopus, Embase, and Science Direct Library.

Results:

28 case reports met inclusion criteria out of an initial 189 articles.

Conclusion:

Acquired selenium deficiency is a causative factor for the development of cardiomyopathy in patients under different conditions, and treatment of these patients with selenium is effective in normalizing cardiac function or reducing cardiac dysfunction. Thus, it is important to include selenium deficiency as a possible cause of cardiomyopathy for diagnosis and treatment purposes.

Keywords: Selenoproteins, selenium deficiency, cardiomyopathy, Ketogenic diet, Parenteral nutrition, Human immunodeficiency virus.

1. INTRODUCTION

Selenium is an essential micronutrient for the human body [1] since it is required for the synthesis of selenocysteine (Sec), which is needed for the synthesis of selenoproteins. Selenoproteins have important pleiotropic biological activities including antioxidant activity, anti-inflammatory activity, and deiodinase activity (which is required for the synthesis of active thyroid hormone) [2]. The process of selenoprotein synthesis involves numerous steps. It begins with serylation of tRNA^{Sec} by seryl-tRNA synthetase to yield seryl-tRNA^{Sec}. The seryl-tRNA^{Sec} is phosphorylated by a phosphoseryl-tRNA^{Sec} kinase to yield phosphoseryl(Sep)-tRNA^{Sec}. The Sec-tRNA^{Sec} is synthesized by Sep-tRNA:Sec-

* Address correspondence to the author at the Department of Medical Sciences, Hackensack Meridian School of Medicine at Seton Hall University, Building 123, 340 Kingsland Street, Nutley, NJ 07110, USA; Tel: 973-275-4309; E-mail: zhiyong.han@shu.edu

tRNA synthase using the phosphoseryl-tRNA^{Sec} and selenophosphate [1]. The Sec-tRNA^{Sec} acts as the Sec donor for the incorporation of Sec into a nascent selenoprotein, as determined by a Sec-specific UGA codon, during translation [3].

The prototype selenoprotein is GPx (glutathione peroxidase), which was characterized as a selenocysteine in 1978 [4]. Since, other selenoproteins with important biological functions have been discovered, including thioredoxin reductases (TRxR) [5], methionine sulfoxide reductase A [6], deiodinases [7], selenoprotein P [8], selenoprotein N [9], selenoprotein M [10], selenoprotein T [11] and selenoprotein S [12]. The important functions of representative selenoproteins are listed in Table 1. Furthermore, studies of animals and humans have linked deficiencies of various selenoproteins and polymorphisms in selenoprotein genes with a medley of diseases including muscle and cardiovascular disorders, hypothyroidism, and epilepsy [3].

Table 1. Normal functions of representative selenoproteins relevant to the cardiovascular system and their corresponding clinical deficient features.

Selenoprotein	Normal Functions	Clinical Features of Deficiency [ref]
Thioredoxin reductase	<ul style="list-style-type: none"> ▪ Disulfide reduction ▪ Maintenance of cellular redox homeostasis 	Dilated Cardiomyopathy in humans [5]
Glutathione peroxidase 1	<ul style="list-style-type: none"> ▪ H₂O₂ signaling ▪ Inactivation of hydroperoxides ▪ Maintenance of cellular redox homeostasis 	Larger myocardial infarct size in a mouse model [76]
Methionine sulfoxide reductase A	<ul style="list-style-type: none"> ▪ Prevention of the buildup of oxidized methionine residues in proteins 	Impaired myocardial contractility when stressed in a mouse model [77]
deiodinases	<ul style="list-style-type: none"> ▪ Activation of T4 to T3 ▪ Degradation of T3 ▪ Regulation of catabolic homeostasis 	Restrictive cardiomyopathy in a mouse model [78]
Selenophosphate Synthetase 2	<ul style="list-style-type: none"> ▪ Synthesis of selenophosphate required for the synthesis of selenoproteins 	No data on clinical features of deficiency [3]
Selenoprotein I	<ul style="list-style-type: none"> ▪ Synthesis of phosphatidylcholine and phosphatidylethanolamine 	No data on clinical features of deficiency [3]
Selenoprotein M	<ul style="list-style-type: none"> ▪ Maintenance of the redox homeostasis in the ER ▪ Facilitation of protein folding in the ER 	No data on clinical features of deficiency [3]
Selenoproteins K and S	<ul style="list-style-type: none"> ▪ Facilitating proteasome-mediated degradation of misfolded proteins in the ER 	No data on clinical features of deficiency [3]

There is a clinical association between selenium deficiency and epilepsy [3]. Thus, infants with intractable epilepsy have significant lower levels of selenium compared with the normal control group ($p < 0.05$) [13]. In animal studies, it has been demonstrated that a selenium deficient diet increased the susceptibility of rats to kainite-induced epileptic seizures [14], and neurological seizures were observed in selenoprotein P knockout mice when they were raised on selenium restricted diet [8, 15].

Multiminicore, a form of congenital muscular dystrophy, characterized by a distinct loss of muscle fiber organization, has been associated with selenium deficiency and/or selenoprotein defects [16]. The etiology has been attributed to mutations in selenoprotein N and ryanodine receptors [10]. Ryanodine receptors are transmembrane proteins in the endoplasmic reticulum and are responsible for releasing calcium from the intracellular stores [17]. It appears that selenoprotein N associates with and facilitates the ryanodine receptors to function properly [18]. It was demonstrated in a zebra fish model that selenoprotein N knockout resulted in disorganized muscle fibers, the hallmark of multiminicore disease [19]. Besides selenoprotein N, selenoproteins M and T also play a vital role in the regulation of calcium-mediated signaling: selenoprotein M attenuates calcium signaling in response to oxidative stress [20], whereas, selenoprotein T increases it [11]. Thus, selenoproteins N, M and T are important regulators of calcium signaling relevant to muscular health and function.

Deiodinases are selenoproteins that play an essential role in thyroid hormone metabolism and function [7]. The biologically active thyroid hormone 3,5,3'-triiodothyronine (T3) is activated by deiodinase from its precursor thyroxine (T4). Specifically, deiodinases types I and II convert T4 to T3 whereas the deiodinase type III inactivates both T4 and T3 by removing specific iodine atoms from T3 and T4 [7]. Since thyroid hormone regulates a plethora of organs metabolic functions including the heart, dysregulation of thyroid hormone levels due to deficiencies of selenium and/or defects in deiodinases increases the risk of pathological cardiovascular perturbations [21].

Reactive oxygen species are known to cause injury to all cell types including the vascular endothelial cells and cardiac myocytes [22]. GPx uses glutathione to detoxify hydroperoxides into water, thereby providing cells anti-oxidant protection [23]. Studies of mice showed that GPx1 inhibited ischemia induced apoptosis of cardiac myocytes [24], and that targeted deletion of GPx1 gene lead to heart and vascular dysfunction [25]. Other forms of GPx, GPx3 and GPx4, provide protection against thrombosis [26] and atherosclerosis [27]. The positive correlation between selenium and GPx activities/expression alludes to selenium's indirect cardiovascular protective role. For example selenium supplementation increases GPx1 and GPx4 activities in vascular endothelial cells, resulting in reduced oxidative stress [28 - 31]. Conversely, long term selenium deficiency leads to decreased GPx expression and activity and cardiovascular damage, which can be reversed by dietary supplementation of selenium [32, 33].

TRxR is crucial for the control of cellular redox homeostasis because it detoxifies peroxides, prevents deleterious disulfide bonds formation within and between biomolecules, reduces thioredoxin, and regulates the redox state of transcription factors, thereby regulating the redox homeostasis in cells [5]. Studies of mice have demonstrated that systemic inactivation of TRxR resulted in embryonic lethality associated with anemic embryos, thinning of the ventricular heart wall and malformation of the heart [34]. Mice studies also show that cardiac tissue-selective knockout of the mitochondrial TRxR gene results in fatal dilated cardiomyopathy [34]. Additionally, cardiomyocyte cell death under ischemic and reperfusion conditions due to failure of thiol regeneration have also been shown in TRxR knockout mice studies [35]. In parallel to these findings, studies of humans have established the protective role of TRxR in the cardiovascular system and identified loss-of-function mutations of TrxR that cause dilated cardiomyopathy in patients [36]. In short, loss of mitochondrial TRxR activity in the heart is a pathogenic factor for the development of dilated cardiomyopathy.

Given the fact that GPx and TRxR are selenoproteins, selenium nutrition plays an important role in the antioxidant systems in the human body. Hence deficiencies of GPx, TRxR and deiodinases secondary to selenium deficiency can result in the pathogenesis of cardiovascular diseases. Thus, the classic demonstration of diseases caused by selenium deficiency is the Keshan disease, which was originally discovered in China with clinical features that are characteristic of dilated cardiomyopathy: cardiogenic shock, cardiac arrhythmias, ECG changes, enlarged heart, and/or congestive heart failure [37]. Epidemiological and population-based intervention studies in China established a causal relationship between dietary deficiency of selenium and the development of Keshan disease [37]. Subsequent case-controlled studies in other countries, such as the one in Finland [38], established an inverse relationship between the serum selenium level and incidence of myocardial infarction and cardiovascular death. Specifically, a low level of serum selenium (< 45 µg/L) was associated with 2-3 times of increased risk for death due to cardiovascular diseases [38]. However, certain epidemiological features of Keshan disease could not be explained solely by selenium deficiency because there are other factors involved [39]. For example, selenium deficiency increases the susceptibility of mice to myocarditis induction by Coxsackie B virus infection [40]. Nevertheless, it is likely that selenium deficiency predisposes an individual to Keshan disease that can be precipitated by other etiological factors and that these factors are likely to act synergistically with selenium deficiency to cause Keshan disease.

At the molecular level, it seems that the best explanation for cardiomyopathy secondary to selenium deficiency is that selenium deficiency causes myopathy as a result of the depletion of GPx and TRxR that protect cardiomyocytes from oxidative damage. Although it is intuitive that selenium deficiency can occur in individuals with malabsorption and/or malnutrition or living in a selenium-deficient environment, there has been no, to the best of our knowledge, systemic review of the published clinical case reports for etiologies of selenium deficiency in relationship to the development of cardiomyopathy. Therefore, in an effort to understand how patients who do not live in selenium deficient areas acquire selenium deficiency and develop selenium-responsive cardiomyopathy, we researched the biomedical literature to identify and review cardiomyopathy cases in which selenium deficiency plays a causative role.

2. METHODS

A systematic search of the published biomedical literature was conducted in PubMed, Scopus, Embase, and Science Direct Library databases for studies investigating cardiomyopathy associated with selenium deficiency. For optimal identification of relevant studies, the search criteria used the following keywords alone and in combination: selenium deficiency, diet, malabsorption, cardiomyopathy, and heart failure. There were no date restrictions applied to the search. For consistency, the same criteria were implemented across all databases. Study selection entailed screening for studies in which selenium deficiency played a role in the etiology of a cardiomyopathy, which was validated on the basis of cardiomyopathy symptoms resolution or reduction after repletion of selenium or selenium deficient level findings

postmortem. Pertinent information from each article was recorded in Tables 2 and 3 without alteration of information or conversion of any selenium values and units reported. Non-English written articles were excluded due our inability to comprehend the language the manuscripts were composed in.

Table 2. Clinical cases of selenium-responsive abnormalities associated with ketogenic diet.

Gender/Age of Patient	Reasons for Using Ketogenic Diet	Duration on Ketogenic Diet	Serum Selenium Level at Time of Symptom Presentation	Symptoms/Diagnostic Finding that Prompted Selenium Analysis	Form of Selenium Treatment	Length of Selenium Treatment that Resolves Symptoms	Reference
M/5 years	Intractable seizures	2.5 months	<25 µg/L (normal >60 µg/L)	Tachycardia, hypotension, cool extremities, poor skin perfusion	Intravenous	10 days	[68]
M/11 years old	Afebrile partial complex seizures	3 years	31.6 µg/L (normal 79-158 µg/L)	No pulse, cardiogenic shock, QT prolongation	None	Patient deceased	[67]
M/7 years old	Intractable epilepsy	3 years	55.2 µg/L (normal 79-158µg/L)	QT prolongation	None	Patient deceased	[67]
F/13 years old	Intractable complex partial seizures	4 years	“non-detectable”	Pale coloring, whitened nail beds and poor hair texture	200µg/day, I.V. 80µg/day, oral	1 month of I.V then switched to oral (length of oral not reported)	[65]

Table 3. Selenium deficiency and cardiovascular abnormalities associated with other etiologies.

Causes of Selenium Deficiency	Patient Information	Gender/Age of Patient	Selenium Status (Normal Values)	Symptoms/Diagnostic Finding that Prompted Selenium Analysis	Administration Route	Length of Selenium Treatment that Resolves Symptoms	Ref
Parenteral Nutrition (PN)	PN was initiated for juvenile polyposis and three-months of refractory skin eruptions. Setting of PN was not reported. No selenium was added to PN. Patient received PN for 5 months	M 18 months	2 µg/dL (10.6-17.4ug/dL)	Xerotic skin changes with irregular shaped erythematous changes on cheek and Cardiomyopathy	Oral	100 µg/day for 24 days and then increased to 200 µg/day	[79]
Parenteral Nutrition	Reason for PN was not reported. Sixteen years on PN at home. Selenium was added to PN but the quantity was not reported.	M 28 years old	62 µg/L (80-230 ug/L)	Heart failure and ventricular premature beats	Not described	Not stated	[80]
Parenteral Nutrition	PN was initiated after ileostomy for nineteen days. Selenium was added to the PN at 32 µg/day.	M 27 years old	0.3 µmol/L (0.8-2umol/L)	Chest pain and tachycardia	Oral	100 µg/day for 3 months	[81]
Parenteral Nutrition	PN was initiated post right hemicolectomy for carcinoid tumor of the terminal ileum. PN administration setting not specified. Selenium was not added to the PN. Length of PN was not reported.	M 61 years old	110 µg/L (110-430 µg/L)	Worsening cardiac heart failure	Intravenous	40 µg/day for 25 days	[82]
Parenteral Nutrition	PN was initiated after ileostomy with resection of cecum and terminal ileum due to diagnosis of chronic idiopathic intestinal pseudoobstruction. PN was given at home. Selenium was not added to the PN. Patient had been on parenteral nutrition for 17 months	F 17 years old	<0.07µmol/L (reference values were not reported)	Incidental findings	Intravenous	100 µg/day for 35 days and then 200 µg/day for 6 months	[74]

(Table 3) *contd.....*

Causes of Selenium Deficiency	Patient Information	Gender/Age of Patient	Selenium Status (Normal Values)	Symptoms/Diagnostic Finding that Prompted Selenium Analysis	Administration Route	Length of Selenium Treatment that Resolves Symptoms	Ref
Parenteral Nutrition	PN was given after first set of operations for small-bowel diverticulosis, incomplete rotation of colon and gastrojejunostomy ulcerations, cardiac symptoms. Setting of PN was not specified. Selenium was not added to the PN. Patient was on PN for 2 years.	M 43 years old	0.033 ng/mg hemoglobin (0.5-1 ng/mg hemoglobin)	Ventricular fibrillation, ventricular extra systole, non-sustained ventricular tachycardia, pulmonary edema, heart failure	Oral	Not described	[83]
Parenteral Nutrition	PN was initiated after intestinal resection of bowel after infarction, patient presented with cardiac symptoms. Patient was on PN for 5 months at home. Selenium was not added to the PN.	M 46 years old	Undetectable blood selenium level	Supraventricular tachycardia	Intravenous	150 µg/day for several weeks	[64]
Parenteral Nutrition	Reasons for PN were not reported. Patient received PN for 3 months. Selenium was not added to the PN	F 49 years old	50 mcg/L (55-130mc g/L)	Tender muscles of upper arms, buttocks, anterior and lateral thighs	Intravenous	200 mcg/day	[84]
Parenteral Nutrition	PN at home for 6 years because severe malnutrition secondary to vomiting and diarrhea. Selenium was not added to the PN.	M 24 years old	12 ng/ml (108 ± 19 ng/ml)	Dyspnea and tachycardia	Not described	Not described	[85]
Parental Nutrition	PN was initiated because of malabsorption due to multiple bowel resection. Patient was on PN at home for 8 years. Selenium was not added to the PN.	M 42 years old	5-12% of normal	Chest pain and dyspnea	Not described	Not described	[86]
Malnutrition	Malnutrition due to total colectomy with end ileostomy from inflammatory bowel disease. Duration of malnutrition was unknown. Patient did not receive any PN prior to hospital presentation	F 53 years old	65 µg/L (80-230 µg/L)	Nausea, vomiting, epigastric pain, increased ileostomy output and tachycardia	Intravenous	100 µg/day for three weeks	[87]
Bariatric Surgery	Bilio-pancreatic diversion for weight loss resulting in severe protein deficiency. Patient presented 9 months post operation with cardiac symptoms	F 55 years old	<0.3 µmol/L (0.7-1.4µmol/L)	Dyspnea, weakness, chest tightness and tachycardia	Oral	Amount not reported, course of 3 weeks	[88]
Chylous Loss	Chylous loss secondary to bilateral chylothorax development post-surgical ablation of lymphangiomatosis, Patient presented with symptoms 10 years after first operation (whiles receiving PN). PN setting was not reported and PN duration was 10 years. Selenium was added at 5µg/kg.	M 11 years old	9.5 µg/L (55-150 µg/L)	Respiratory failure and hypotonia with leg weakness	Intravenous	110 µg/day for 8 days	[89]
Malnutrition	Malnutrition secondary to a diet consistent of only grits, sausage, beans, frankfurter, pork and Kool-Aid. Two years of malnutrition before onset of symptoms	F 2 years old	0.035 µg/ml (0.07-0.16 µg/ml)	Dyspnea and weakness	Oral	2 µg/day for 4 weeks	[90]
Chronic Diarrhea	Reason and duration for diarrhea not reported by authors.	M 15 months	9.1 µg/L (55-103 µg/L)	Labored breathing, tachypnea, weight loss and poor appetite	Intravenous	2 µg/kg/day for 3-4 months	[91]
Malnutrition	Reason for malnutrition not reported by authors. Two years of malnutrition before onset of cardiac symptoms	F 55 years old	38 µg/L (79-326 µg/L)	Dyspnea, weakness and repetitive syncope	Intravenous	100 µg/day for 3 weeks	[92]

(Table 3) contd.....

Causes of Selenium Deficiency	Patient Information	Gender/Age of Patient	Selenium Status (Normal Values)	Symptoms/Diagnostic Finding that Prompted Selenium Analysis	Administration Route	Length of Selenium Treatment that Resolves Symptoms	Ref
Chronic Diarrhea	Diarrhea due to Crohn's disease. Duration of diarrhea till cardiac symptom development was not reported.	F 22 years old	4 µg% (6-16 µg%)	Weight loss, malaise and tachycardia	Intravenous	200 µg/day for several weeks	[93]
Chronic Diarrhea	Diarrhea for a week due to <i>C. Difficile colitis</i> . Patient did not receive PN prior to hospital presentation	F 47 years old	0.34 µmol/L (0.75-1.5µmol/L)	Diarrhea	Intravenous	200 µg/day for 48 hours and then 100 µg/day for 10 days	[94]
Bariatric Surgery	Whipple for presumed carcinoma of pancreas (no histopathological confirmation). A Roux-en-Y gastric bypass procedure due to stricture of choledochojunostomy. Post-surgical duration before symptoms appeared was not reported.	F 42 years old	0.7 µmol/L (0.9-2.0 µmol/L)	Diarrhea and vomiting	Not described	Not applicable	[95]
Bariatric Surgery	Roux-en-Y bypass for medically complicated obesity. Patient presented with symptoms 4 years post the by-pass surgery	F 66 years old	41 ng/ml (95-165 ng/ml)	Weakness and poor oral intake	Oral	50 µg/day for 1 week	[96]
Bariatric Surgery	Roux-en-Y bypass to manage obesity. Patient presented with symptoms 9 months post the by-pass surgery.	F 40 years old	53 µg/L (89-150 µg/L)	Dyspnea and bilateral lower extremity pitting edema	Oral	2 µg/kg/day for 3 weeks	[97]
HIV	Patient presented with symptoms 2 years after HIV diagnosis	M 27 years old	24 µg/L (83 ± 17 µg/L)	Tachycardia	Intravenous	Amount not reported	[98]
HIV	Patient infected by HIV <i>via</i> maternal birth and presented with cardiac symptoms after 6 years of life.	M 6 years old	29 µg/L (90-170 µg/L)	Tachycardia, Heart failure and respiratory distress	Oral	4 µg/kg/day for 3 weeks	[99]
RDEB	Patient was diagnosed with RDEB at 4 years old. At 6.3 years supplementary selenium (dose and form were not reported) was given for incidental low selenium of 0.53µmol/L. Patient remained deficient due to poor household conditions and 2 years later presented with dyspneic symptoms	M 6 years old	0.7 µmol/L (0.7-1.7 µmol/L)	Breathlessness and cough	Oral	Dose not reported; course of 4 months	[75]
RDEB	Patient was diagnosed with RDEB at 3.5 years, and presented with cardiac symptoms 8.5 years later	M 12 years old	0.7 µmol/L (0.7-1.7 µmol/L)	Breathlessness and cough	Oral	Dose not reported; course of 4 months	[75]
Cystic Fibrosis	Admitted to the hospital at 6.5 months for loose stools, edema and failure to thrive, and a diagnosis of cystic fibrosis was made at that time. Low selenium found during workup. Placed on parenteral nutrition. No information on selenium in the PN. After two weeks of hospital stay patient became tachypneic	M 6.5 months	5 µg/dL (10-20 µg/dL)	Tachypnea	Intravenous	100 µg/day for 3 weeks	[100]

3. RESULTS

As shown in Fig. (1), our search strategy yielded a total of 189 studies. We retrieved 31 studies of which 28 met our criteria and were included in our report. Tables 2 and 3 contain relevant information regarding each patient's gender, age, cause of selenium deficiency, selenium status, symptoms that prompted selenium analysis, form of selenium used for treatment, and length of selenium treatment to resolve symptoms.

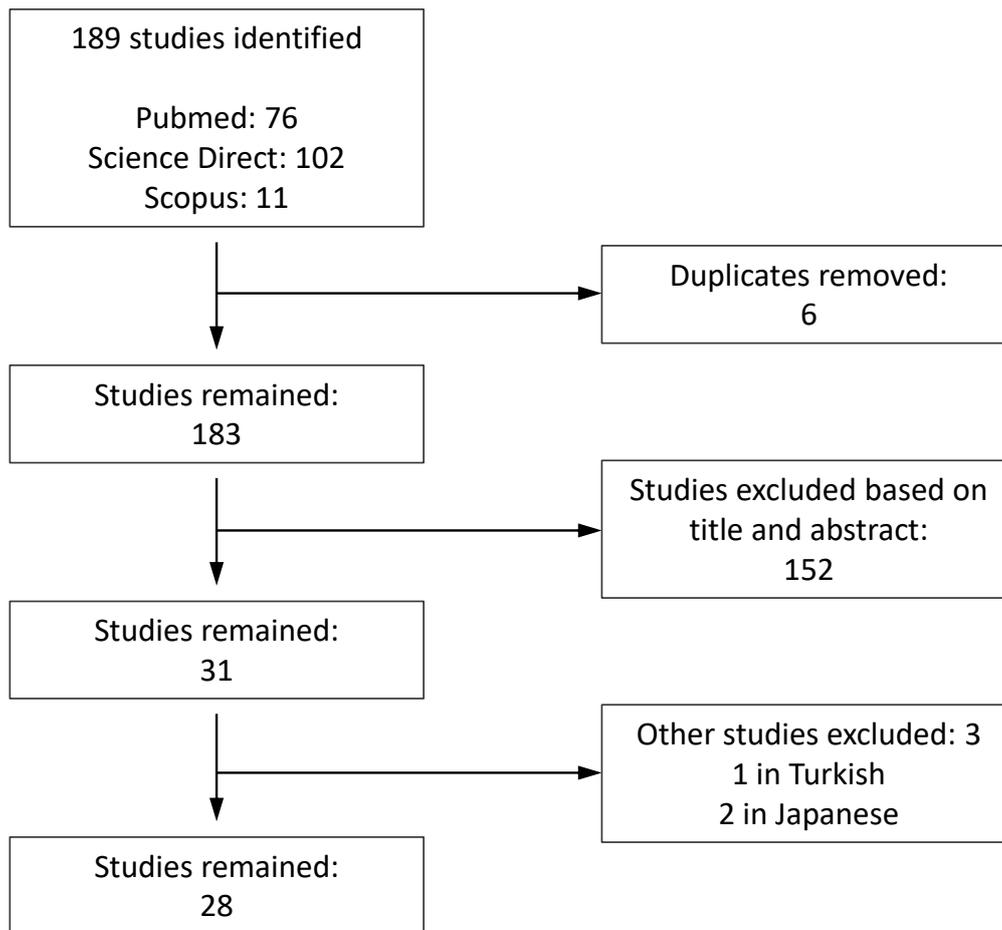


Fig. (1). Flowchart of study selection.

3.1. Ketogenic Diet Causes Selenium Deficiency and Cardiomyopathy

The ketogenic diet is a low-carb diet that substantially changes the energy fuel partition in the body. The classic ketogenic diet is based on a 4:1 of fat to carbohydrate ratio [41]. The ketogenic diet has been proven to be beneficial to patients with drug-resistant epilepsy [42]. One study showed that 38% children in the study who had been placed on ketogenic diet for three months experienced a reduction in seizures by over 50% compared to 6% in the control group [43]. In the same study, 5 children in the ketogenic diet group experienced a reduction in seizures by 90% compared to the control [43]. In another study, 55% children with refractory epilepsy became seizure free after they had been placed on a ketogenic diet that was 80% fat in terms of total calorie [44]. However, ketogenic diet is not entirely safe; its high fat content and low carbohydrate intake may lead to hyperlipidemia, atherosclerosis, and hypoglycemia [45, 46]. In this review, we identified four cases of selenium-responsive pediatric cardiomyopathy that resulted from selenium deficiency due to the use of ketogenic diet to manage their epilepsy (Table 2). Selenium deficiency as the cause of cardiomyopathy was validated by the fact that treatment of these patients with selenium supplement normalized their cardiac functions.

3.2. Selenium Deficiency and Cardiomyopathy Associated with Gastrointestinal Disorders

Intestinal failure, due to functional or anatomic changes, results in reduced absorption of macronutrients and micronutrient below the minimum threshold level. Short Bowel Syndrome (SBS) [47] is a condition that occurs when less than 200 cm of the small intestine remains because of bowel disease, congenital defect or surgery [48]. In SBS/intestinal failure, the body is unable to absorb sufficient minerals, nutrients, water and vitamins from the diet to sustain life [47] and as a result, Parenteral Nutrition (PN) must be administered to curtail malnutrition [49]. Parenteral nutrition aims to provide nutritional requirements in circumstances where full enteral feeds will be delayed or inadequate [49]. The process calls for an intravenous infusion of macronutrients, micronutrients, and electrolytes. However, PN can cause side effects. The most common side effects include liver dysfunction (cholestasis, steatosis,

steatohepatitis and liver cirrhosis) [50] and loss of bone mineral density [51]. Selenium deficiency is another finding observed in PN. With the usage of PN as treatments for the increased incidence of SBS/intestinal failure [52 - 54]. In this review, we identified 23 cases of selenium-responsive cardiomyopathy due to selenium deficiency secondary to a gastrointestinal etiology (Table 3).

3.3. Selenium Deficiency and Cardiomyopathy in Patients with AIDS without HAART

Heart failure among patients infected with HIV is common [55]. In the pre-HAART (highly active antiretroviral therapy) era, HIV associated cardiomyopathy was observed in patients with severe AIDS [55]. Thus, in a study involving 3,000 pediatric AIDS patients, HAART decreased cardiomyopathy from 25.6 cases per 1000 person per year to 3.9 cases [56]. It is important to note that most studies investigating decrease in HIV cardiomyopathy due to HAART are conducted in Europe or in America [57]. However, AIDS patients in economically impoverished regions, such as the Sub-Saharan Africa [58], have very limited access to HAART. More specifically, an approximate 32% increase in the prevalence of HIV cardiomyopathy and related mortality was observed in developing nations where HAART access is limited, and thus pathogenic impact of nutritional factors is more significant [59]. Although most studies of the relationship between serum selenium levels and HIV infection in humans measured the effect of selenium on CD4 cell counts and/or HIV seropositivity, there is some evidence for a relationship between selenium deficiency and development of HIV associated cardiomyopathy. Furthermore, selenium supplementation appears to improve the cardiac function in AIDS patients. For example, a prospective multicenter study of 416 HIV positive patients in Rwanda who had no access to HAART and did not have a documented history of cardiovascular disease revealed a significant association of low serum level of selenium with the development of cardiomyopathy [60]. In this review, we identified three studies of HIV associated selenium-responsive cardiomyopathy that result from selenium deficiency (Table 3). The findings of one particular report by Zazzo *et al.* [61] is not included in the Table because certain patients information and lab values (patient gender, age, and serum selenium values) were not reported. Nevertheless, it is important to note that Zazzo *et al.* reported the effect of selenium treatment of eight AIDS patients with nonobstructive cardiomyopathy. This group of patients were diagnosed according to changes in the value of left ventricular shortening fraction, and low serum selenium. These patients were treated with oral sodium selenite (800 µg/day for 15 days and then 400 µg/day for 8 days). Weekly evaluations showed that the treatment normalized left ventricular function in six patients, one patient died on the 15th day, and one patient also had a thiamine deficiency [61]. Nevertheless, the response to selenium treatment by the AIDS patients listed in Table 3 and reported by Zazzo *et al.* demonstrated a causal relationship between selenium deficiency and HIV associated cardiomyopathy.

3.4. Selenium Deficiency and Cardiomyopathy in a Patient with Dystrophic Epidermolysis Bullosa

Recessive dystrophic epidermolysis bullosa (RDEB) is a condition in which the formation of anchoring fibril at the dermal-epidermal junction is disrupted and it is thought to be brought about by mutations in type VII collagen [62]. Patients with RDEB develop skin blister and skin fragility due to minimal trauma [62] and are at risk of developing cardiomyopathy if they acquire selenium deficiency [63]. This review identified one case report of selenium-responsive cardiomyopathy due to selenium deficiency in a RDEB patient (Table 3).

4. DISCUSSION

Keshan disease is a well-documented dilated cardiomyopathy described as focal myocardial necrosis with normal coronary arteries [64]. It was an endemic disease with high incidence in regions where the soil has little selenium [64]. Dietary sources of selenium include seafood, meat and cereals [65]. This portends that human selenium levels is contingent on the type of food intake and source of cereal – whether the grains for cereal production are grown in selenium rich soil or deficient in selenium [65]. The ketogenic diet, which consists mostly of fat in addition to some fish/eggs/meats, has insufficient amounts of selenium compared to a more balanced diet [66]. For example, Bergqvist *et al.* conducted a retrospective analysis of the ketogenic diet and showed a deficiency in selenium [65]. In the case report by Bank *et al.*, although they did not report an analysis of their patient's ketogenic diet, their post mortem cardiomyocyte examination was consistent with findings observed in the context of selenium deficiency [67]. Similarly, although Sirikonda *et al.* did not report the ketogenic diet content of their patient, their diagnosis of the patient with selenium deficiency-induced cardiomyopathy was supported by the fact that the patient had low serum selenium level and that selenium supplementation and termination of the ketogenic diet resulted in cardiac improvement [68].

Similar to ketogenic diet, PN may also be low in selenium [69]. The amount of selenium provided in PN is typically 20-60 µg/day, which is inadequate [70, 71]. An increase of selenium in PN has been proposed to 60-100 µg/day [70, 71], given selenium requirements are increased in malabsorptive states [71]. Regardless of this adjustment, higher doses of selenium in parenteral nutrition might still be warranted for patients with SBS and non-SBS [71]. In a study conducted by Milan *et al.*, 68 patients receiving long term care for SBS using parenteral nutrition had significant decline in serum selenium levels [72]. On the contrary, other trace elements, such as zinc, copper and iron, had no significant difference between patients with PN and control subjects [72], suggesting that the selenium provided by the conventional PN is insufficient and explaining why selenium deficiency was observed in a significant number of patients on PN. The cases we reviewed involved patients with lower nutritional status stemming from various etiologies such as lack or reduced selenium in their oral/parenteral diet and numerous gastrointestinal pathologies that resulted in intestinal failure. Given that sick patients tend to have a poor appetite and hence lower nutritional status, poor selenium intake seems an important determinant for the selenium deficiency of the patients in Tables 2 and 3. Thus, it is important to make certain that PN is supplemented with sufficient selenium and that the selenium levels of patients need to be continuously monitored to prevent the development of selenium deficiency related conditions including, but not limited to, cardiomyopathy.

Patients suffering from AIDS are another group of patients who are at risk of selenium deficiency. Some AIDS patients developed HIV associated cardiac abnormalities similar to those found in Keshan disease [73]. HIV causes impaired systolic function through proinflammatory cytokines such as tumor necrosis factor and IL-1β [55]. In conjunction with these findings, there are reports of sudden cardiac death in selenium deficiency patients triggered by sepsis [74]. However, the pathophysiology of how infections alters the immune systems response in selenium deficient patients leading to cardiomyopathy remains elusive. The change in the immune systems reaction may underlie the susceptibility of cardiomyopathies of individuals with inadequate selenium nutrition.

We have identified two cases of cardiomyopathy due to selenium deficiency associated with RDEB reported by Melville *et al.* [75]. Although, according to the report, the patients involved were malnourished, numerous patients with RDEB (14 to 25 patients) had reduced serum selenium levels without cardiomyopathy [75]. Thus, it is possible that patients with RDEB are at risk of developing selenium deficiency, which, if worsens, can lead to cardiomyopathy. Thus, Melville *et al.* recommended that patients with severe RDEB should be examined carefully for their nutritional intake including selenium and with regular echocardiographic screening for signs of cardiomyopathy.

It is important to note that the selenium status of the patients in Tables 2 and 3 was determined by serum selenium levels, and that majority of the cases involved sick patients who might have had other unknown confounding factors that cause selenium deficiency. An alternative method of assessing selenium status is measuring intracellular concentrations or the activities of selenoproteins [5, 27, 33]. Ideally, the selenium status should be monitored by multiple methods that determine not only the serum level but also intracellular level and the activities of selenoproteins, such as glutathione peroxidase in cells. Nevertheless, the fact that the cardiomyopathy symptoms were alleviated after administration of selenium in most patients reviewed suggests that the measurement of serum selenium level is a useful way to determine selenium status of patients with cardiomyopathy symptoms.

The cases of cardiovascular dysfunction listed in Table 2 and 3 represent selenium-responsive cases and furthermore show distinctive patient populations who are at risk of developing cardiovascular dysfunction due to selenium deficiency. However, it is possible that selenium deficiency in populations of patients with these diseases and/or other diseases is underreported because those patients who have yet to present with cardiovascular dysfunction are unlikely to receive selenium status analysis. Therefore, it is important that physicians think about including selenium status analysis for patients with certain diseases (IBS, AIDS, and RDEB, for example) and/or receiving certain treatment, such as ketogenic diet and parenteral nutrition. Doing so is important because physicians can take simple management – selenium supplementation – to prevent the development of cardiovascular dysfunctions, such as cardiomyopathy, in these patients.

CONCLUSION

These cases in the literature emphasize the need for considering selenium deficiency as a potential cause of the development of cardiomyopathy in patients in various diseases states and treatments. We hope to draw attention to implement preventative measures of selenium deficiency-induced cardiomyopathy in these clinical contexts. Moreover, we hope to spark more investigation into the pathophysiology of selenium induced cardiomyopathy.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise

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Nigel Amankwah: Performed research, collected data, organized and analyzed data, wrote paper

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