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ORIGINAL ARTICLE

The Role of Selenium Deficiency in Dilated Cardiomyopathy

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ABSTRACT

Background: It has been speculated that trace elements may play a role in the pathogenesis of dilated cardiomyopathy (DCM). In the present study, we aimed to assess serum concentrations of selenium (Se) in pediatric patients with idiopathic dilated cardiomyopathy (IDC) and to evaluate the correlation between serum Se concentrations and echocardiographic parameters. **Methods:** This study included 16 patients with IDC and 16 healthy controls. Serum level of selenium was measured by ELIZA method. Echocardiographic parameters including ejection fraction and fractional shortening were measured in all patients with IDC in order to evaluate its correlation with serum Se concentrations. **Results:** Serum concentration of Se in IDC patients was significantly lower than in healthy controls ($p<0.05$). Relationships of the serum Se levels with echocardiographic parameters (FS) and few clinical parameters were statistically significant. **Conclusions:** The present study confirmed that IDC is associated with decreased serum Se concentrations. This change in Se may play an important role in the pathogenesis of myocardial damage in IDC.

Key words: Selenium; echocardiographic parameter; idiopathic dilated cardiomyopathy

INTRODUCTION

Idiopathic dilated cardiomyopathy (IDC) is a disease of unknown cause. It leads to enlargement of the heart which does not pump properly. It is the most common cause of heart transplantation [1]. IDC is characterized by dilatation or hypertrophy of cardiac chambers. Dilatation is more common than hypertrophy, and the left ventricle (LV) is affected more than the right ventricle (RV) [2]. Selenium (Se), a trace element, is an essential micronutrient for organisms ranging from bacteria to humans. Most of the Se in tissues is present in two forms, selenocysteine and selenomethionine [3]. The principal dietary forms of Se are selenoaminoacids. Selenomethionine is derived from plants while selenocysteine is derived from animal sources. The major role of Se in human body is as antioxidant for protection against oxidative stress initiated by excess reactive oxygen species (ROS) and reactive nitrogen species (NOS). [ROS include; superoxide anion (O2) hydrogen peroxide (H2O2), and hydroxyl radical (OH)] [4]. The major role of Se in mammalian is incorporation into the active site of glutathione peroxidase enzyme (GSHPX) in the cytosol and mitochondria for protection biomembranes against destruction [5]. Erythrocyte GSHPX contains four Se atoms in the form of selenocysteine that are essential for its biological activity [6]. GSHPX catalyzes the breakdown of H2O2, phospholipid hydroperoxides and other free hydroperoxides.

Se deficiency leads to decreased GSHPX activity. Therefore, trace elements like Se, Zn and Cu have an antioxidant function in many essential enzyme system [7]. Deficiency of these enzymes leads to reaction of O2 with (H2O2) forming (OH-) which destroys cell membrane [8]. Increased ROS production can result in myocyte hypertrophy, apoptosis and interstitial fibrosis which lead to decreased cardiac functions and progression to heart failure [9]. GSHPX (Selenium-containing protein) functions by removing H2O2 and detoxifies the lipid hydroperoxides [10]. Therefore, Se deficiency has been implicated as a causal factor in some cases of congestive cardiomyopathies and increased cardiovascular complications [11]. In China, such deficiency has been involved in the pathogenesis of keshan disease, a well-described cardiomyopathy [12]. Iatrogenic causes of Se deficiency include parenteral and enteral nutrition. Low plasma Se is also found in malabsorption, cystic fibrosis, and other varied clinical disorder [13]. The Se content of foods varies widely and is directly related to food protein content and the soil Se content in the area where the food was produced. The recommended daily intake of Se for men and women is 70 and 55 μg/day, respectively [6]. The aim of this study is to evaluate the status of Se in Egyptian pediatric patients with IDC and to investigate potential relation between serum Se concentrations and the echocardiographic parameters.

METHODS

We studied 16 patients with idiopathic dilated cardiomyopathy (IDC) (5 males,11 females, mean age 1.8 +1.4 years) who were admitted to Pediatrics Department, Zagazig University Hospitals. The control subjects in this study included 16 healthy volunteers (4 males,12 females, mean age 2 +1.1years). Written informed consent was obtained from all participants and the study was approved by the research ethical committee of Faculty of Medicine, Zagazig University. The work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

The diagnosis of IDC was based on the WHO/ISFC criteria [14]. It was made when the echocardiogram showed a LV ejection fraction (less than 50%). Patients were excluded from the study if they had a history of renal disease, thyrotoxicosis, sickle cell anemia, severe hypertension, or other known causes of dilated cardiomyopathy (DCM).

Three milliliters of a blood sample were aspirated from peripheral vein of each patient and control subject and was transferred to plain test tube, left to clot and then centrifuged for 10 minutes at 3000 r.p.m. The clear serum was stored at -20 ºC until used for measurement of the concentration of selenium (Se). Analyses of serum samples were carried out by using ELISA method by assaying Human SELENBP1 level in the sample, useing Purified Human SELENBP1 antibody. Addition of tetramethylbenzidine substrate solution and the color change was measured spectrophotometrically at a wavelength of 450 nm. The concentration of Human SELENBP1 in the samples is then determined by comparing the O.D. of the samples to the standard curve.

Echocardiographic Evaluation:

Echocardiographic parameters including; left ventricular ejection fraction and LV fractional shortening were measured in all IDC patients by consultant pediatric cardiologist of echocardiographic unit by M-mode echocardiography.

Statistical analysis

The collected data were computerized and statistically analyzed using SPSS program (Statistical Package for Social Science) version 24. Quantitative data were expressed as mean ± SD (Standard deviation) for parametric and median and range for non-parametric data. The linear regression test was applied for the correlation between different parameters and the significance of the r-values was checked using t-test. P-values of less than (0.05) were considered significant.

RESULTS

Table 1 shows comparison between patient and control groups regarding demographic data (age and gender). Mean (years) ±SD of age in DCM group was 1.8±1.4 and Mean (years) ±SD of control group was 2 ±1.1. Regarding sex the patients of DCM group was 11 female and 5 male while was 12 female and 4 male in healthy control group. No significant difference in age and sex between both groups. ($p > 0.05$). **Table 2** summarizes the mean (±SD) of serum levels of Se element in the DCM patients and in the controls. The mean (±SD) serum Se level in the healthy controls of present study was 80.4 ± 24.1ng/ml while mean (±SD) serum Se level in the patients group was 54.4 ± 24.2 ng/ml. Patients with IDC had lower serum Se concentrations than the controls. Significant difference in selenium level between the two-studied groups is present ($p<0.05$). **Table 3** shows Correlation analysis between serum selenium level and measured echocardiographic parameters (EF and FS) in the DCM group . Positive correlation is present between serum selenium level and fraction shortening ($p<0.05$). **Table 4** shows Correlation analysis between serum selenium level and laboratory parameters (CBC, livre function test and renal function test) in the DCM group. No significant correlation between serum selenium level and different laboratory value except serum albumin, T. protein and creatinine level.

Table 1. Comparison between the studied groups regarding demographic data.

		Group				**Test**	**P**
		DCM		Control			
		No	%	No	%		
Age group	Child	5.00	31.3%	4.00	25.0%	0.01	0.998
	Infant	11.00	68.8%	12.00	75.0%		
	Mean (years) ±SD	1.8±1.4		2 ±1.1		-2.4*	0.076
	Median (years) (range)	1 (0.2-10)		2 (0.4-12)			
Gender	M	5.00	31.2%	4.00	25.0%	0.01	0.998
	F	11.00	68.8%	12.00	75.0%		

Table 2. Comparison both groups regarding serum selenium level

		Group				**X^2**	**p**
		DCM		Control			
		No	%	No	%		
Selenium Level	Low	10.00	62.5%	4.00	25.0%	4.5	0.037
	Normal	6.00	37.5%	12.00	75.0%		
		Mean±SD	Median (range)	Mean±SD	Median (range)	MW*	P
Selenium, ng/mL		54.4 ± 24.2	44 (25-90)	80.4 ± 24.1	87.5 (40-120)	-2.9	0.003

Table 3. Correlations between serum selenium Level and echocardiography parameters in the DCM group

	DCM	
	R	P
EF	0.282	0.290
FS	0.827	**0.014**

Table 4. Correlations between selenium level and laboratory parameters in the DCM group

	DCM	
	r	P
WBC	-0.025	0.926
PLT	0.099	0.715
HB	0.187	0.487
Albumin	0.815	<0.001
T.protin	0.588	0.016
ALT	0.051	0.852
AST	0.151	0.576
T.Bilirubin	0.148	0.584
D.bil	0.247	0.356
BUN	-0.184	0.495
Cr.	0.505	0.046

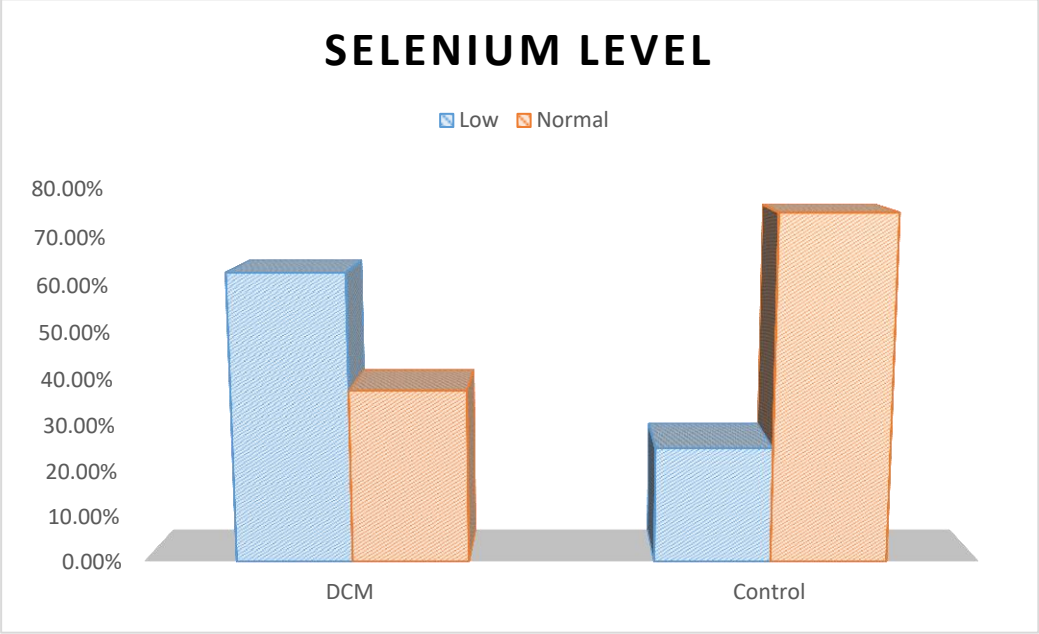

Fig 1.Comparison between selenium level in both groups

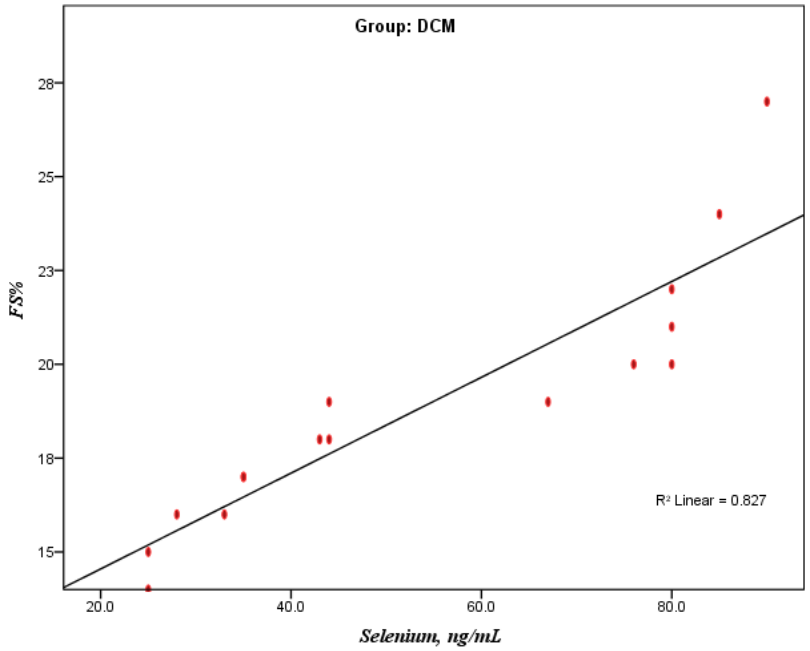

Fig 2. Correlation of Selenium, ng/ml and FS in the DCM group,

DISCUSSION

Trace elements are known to have a key role in myocardial metabolism. Trace elements such as Se may be protective against heart diseases. On the other hand, the Se deficiency causes cardiomyopathy. As a result of the depletion of essential enzymes such as GSHPX, which protect cell membranes from damage by ROS [8].

The mean of serum Se level in Egyptian healthy controls of the present study was (80.4 ± 24.1 ng/ml). It was higher than that reported by chen et al., [15] who recorded mean ±SD of serum Se level in Egyptian subjects around (54±79) ng/ml This difference may be interpreted depending on the region from where the control samples are collected.

(Table 2) shows10 Patients (62.5%) have low selenium level and 6 patients (37.5%) have normal level in dilated cardiomyopathy group while in control group 4 patients (25%) have low selenium level and 12 patients (75%) have normal value. There was significant difference in mean value of serum selenium in both patients and control group. This is consistent with Basil et al., [16] and Koşar et al. [17] who reported that significant difference in mean of serum se value of patients of DCM and healthy control group, also our results was matched with Frustaci et al., [18] who studied group of patients having intestinal malabsorption and developed DCM and found significant decrease in mean value of selenium of patients with DCM and control group. Bergqvist et al., [19] studied a group of epileptic patients, taking ketogenic diets and developed DCM, and they reported significant decrease of mean value of serum selenium in patients than control group. This change in serum selenium may play an important role in the pathogenesis of myocardial damage as selenium is an integral and necessary part of the enzyme glutathione peroxidase. This enzyme acts to catalyse active oxygen species thereby protecting cells from damage of free radicals, also Se-associated proteins STAT3 and MAPK1, the proteins involved in HIF-1 signaling pathway and apoptosis pathway, may play significant roles in the pathogenesis of KD as explained by Wang et al., [20]. In contrast to our study Raines et al., [21] in Saudi Arabian found no significant difference of mean of serum selenium level of both patients and control group and Da cunha et al., [22]

documented no significant difference of mean of serum Se level. This may be due to different population and sample size as Selenium level found in the population depends on its presence in the soil and in the food chain [23].

Positive correlation between selenium level and FS (table 3) and this matched with Oster et al., [24] who reported that there is positive correlation between Se level and cardiac function (EF) .This explained by Beck et al., [25] who reported that reduced selenium affect expression of GPX1 which is antioxidant, protecting against CVB3-induced myocarditis which usually lead to DCM and reduced cardiac function. But Basil et al., [16], Koşar et al., [17] and Da cunha et al., [22] reported no correlation was observed between serum selenium levels and left ventricular ejection fraction .

Positive correlation between serum selenium level and albumin level (r 0.815) ($p<0.001$) table (4). This may refer to significant association between malnutrition and low selenium level in our study. So selenium deficiency may be the cause of DCM in these patients group. This match with study done by Bergqvist et al., [19] on group of patients taking ketogenic diet, which lead to malnutrition and was deficient of selenium and the patients develop cardiomyopathy.

This finding raises the question of the possible benefit of Se replacement in patients with IDC refractory to conventional therapeutic schemes.

CONCLUSION

This study confirmed that pediatric patient with IDC have had decreased serum Se concentrations. This change in Se serum concentration may play an important role in the pathogenesis of myocardial damage in IDC. Further studies are required to evaluate the effect of an appropriate dose of an oral Se supplement in such patients, in particular, those of an early diagnosis.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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REFERENCES

1. **1.Braunwald E, Bristow MR,** congestive heart failure: fifty years of progress.circulation(2000);102:IV14.
2. **Dec GW, Fuster V**. Idiopathic dilated cardiomyopathy. N Engl. J Med.1994; 331: 1564-1575.
3. **Stadtman TC.Selenium biochemistry.Ann.Rev**. Biochemistry, 1996; 65:83-100.
4. **Rayman MP.**The importance of selenium in human health Lancet.2000; 356 :233-241
5. **Neve J**. Human selenium supplementation as assessed by changes in blood selenium concentration and glutathione peroxidase activity .Jour Trace Elem Med Boil.1995; 51:1208-1215.
6. **Burtis CA, Ashwood ER**. Trace elements .In:Tietz textbook of clinical chemistry. 1999. W.B. saunders company .3rd edition: 1029-1055.
7. **Spallholz J E,Boylan LM ,Larsen HS**. Advances in understanding selenium's role in the immune system .Ann NY Acact Sci .1990; 587:123-139.
8. **kosar F ,Sahin I,Taskapan C, Küçükbay Z, Güllü H**. Trace element status (Se,Zn,and Cu) in heart failure.. Anadolu kardiyol Derg .2006; 6 (3): 216-220.
9. **kinugawa S ,Tsutsui H ,Hayashidani S , Ide T, Suematsu N, Satoh S, et al .,** Treatment with dimethyl-thiourea prevents left ventricular remodeling and failure after experimental myocardial infarction in mice :role of oxidative stress. Circ Res.2000; 87:392-398.
10. **Shiomi T ,Tsutsui H ,Matsusaka H , Murakami K ,Hayashidani S , Ikeuchi M, et al.,** Overexpression of glutathione peroxidase prevents left ventricular remodeling and failure after myocardial infarction in mice .Circulation. 2004; 3: 544-549.
11. **Neve J.** Selenium as a risk factor for cardiovascular diseases. Jour cardiovascular Risk. 1996; 3:42-47.
12. **Xu GL,Wang SC,Gu BQ , Yang YX, Song HB, Xue WL, et al.,** Further investigation on the role of selenium deficiency in the etiology and pathogenesis of keshan disease. Biomed Environ Sci.1997; 10:316-326.
13. **Lockitch,G.** Selenium : clinical significance and analytical concepts. Crit. Rev. Clin. Lab. Sci.1989; 27:483-541.
14. **Richardson P, Mckenna W,Bristow M.** Report of the 1995 World Health Organization/Iternational Society and Federation of Cardiology. Task force on

the definition and classification of cardiomyopathies.circulation.1996; 93:841-842

15. **Chen X, Yang G, Chen J, Chen X, Wen Z, Ge K.:** SELENIUM AND CARDIOMYOPATHY (KESHAN DISEASE) Acta Pharmacologica et Toxicologica journal **(2009);** 59: 325-330
16. **Basil O.M. Saleh, Lewai S. Abdulaziz, Thair I. Al-Bajjar** Selenium Status and Echocardiographic Parameters in Iraqi Patients with Idiopathic Dilated Cardiomyopathy. THE IRAQI POSTGRADUATE MEDICAL JOURNAL **(2007);** 6 (1): 45-48
17. **Koşar F, Sahin I, Taşkapan C, Küçükbay Z, Güllü H.** "Trace element status (Se, Zn, Cu) in heart failure". the Anatolian journal of cardiology **(2006);** 6 (3): 216–20.
18. **Andrea Frustaci, Enrico Sabbioni, Salvador Fortaner, Massimo Farina, Ciriolo MR, Russo MA, et al.,** " Selenium- and zinc-deficient cardiomyopathy in human intestinal malabsorption: preliminary results of selenium/zinc infusion". *European Journal of Heart Failure* **(2012);** 14 : 202–210
19. **Bergqvist, A. G. C., Chee, C. M., Lutchka, L., Rychik, J., & Stallings, V. A.** Selenium deficiency associated with cardiomyopathy: a complication of the ketogenic diet. *Epilepsia*, **(2003) ;** *44* (4): 618–620.
20. **Sen Wang , Yanyan Lv, Yingting Wang ,Peiru Du1, Wuhong Tan1, Mikko J. et al.,** Preliminary quantitative proteomics analysis in chronic and latent Keshan disease by iTRAQ labeling approach. *Oncotarget.* **(2017);** 8 (62): 105761–105774.
21. **Raines, D. A., Kinsara, A. J., Fawzy, M. E., Vasudevan, S., Mohamed, G. E., Legayada, E. S., et al.,** Plasma and urinary selenium in Saudi Arabian patients with dilated cardiomyopathy. *Biological Trace Element Research*. **(1999);** 69: 59-71.
22. **Da cunha S ,Filho FMA ,Da Cunha Bastos VLF , Antelo DS, De Souz MM**: Thiamin ,Selenium and Copper levels in patients with idiopathic dilated cardiomyopathy taking diuretics. *Araq Bras Cardiol* **(2002);** *79*: 460-465.
23. **Chen, X., Xu, J., Liu, D., Sun, Y., Qian, G., Xu, S., et al.,** The aggravating effect of selenium deficiency on T-2 toxin-induced damage on primary cardiomyocyte results from a reduction of protective autophagy. *Chemico-Biological Interactions*, (2019); 300: 27–34.
24. **Oster, O., Prellwitz, W., Kasper, W., & Meinertz, T.** Congestive cardiomyopathy and the selenium content of serum. *Clinica Chimica Acta*, **(1983);** 128(1): 125–132.
25. **Beck, M. a, Levander, O. a, & Handy, J.** Oxidative Stress Mediated by Trace Elements Selenium Deficiency and Viral Infection 1. *Journal of Nutrition*, **(2003);** 133(7): 1463–1467.

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