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Association between dietary selenium and zinc intake and risk of dilated cardiomyopathy in children: a case-control study

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Abstract

Background Dilated cardiomyopathy (DCMP) is characterized by the enlargement and weakening of the heart and is a major cause of heart failure in children. Infection and nutritional deficiencies are culprits for DCMP. Zinc is an important nutrient for human health due to its anti-oxidant effect that protects cell against oxidative damage. This case-control study aimed to investigate the relationship between dietary intake of zinc and selenium and the risk of DCMP in pediatric patients.

Methods A total of 36 DCMP patients and 72 matched controls were recruited, and their dietary intakes were assessed via a validated food frequency questionnaire. We used chi-square and sample T-test for qualitative and quantitative variables, respectively. Logistic regression analysis was applied to assess the relationship between selenium and zinc intake with the risk of DCMP.

Results After fully adjusting for confounding factors, analyses showed that selenium (OR=0.19, CI=0.057–0.069, P trend < 0.011) and zinc (OR=0.12, CI=0.035–0.046, P trend < 0.002) intake were strongly associated with 81% and 88% lower risk of pediatric DCMP, respectively.

Conclusions This study highlights the protective role of adequate dietary intake of selenium and zinc in decreasing the risk of DCMP in children. Malnutrition may exacerbate the condition and addressing these micronutrient deficiencies may improve the cardiac function. Further studies are recommended to detect the underlying mechanisms and dietary recommendations for DCMP prevention.

Keywords Dilated cardiomyopathy, Selenium, Zinc, Pediatrics, Case-control study

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Introduction

Dilated cardiomyopathy (DCMP) is a condition characterized by systolic dysfunction and biventricular or left ventricle dilation in the lack of predisposing factors such as coronary artery disease, hypertension or valvular disorders which cause systolic dysfunction [1]. DCMP usually begins in the left ventricle by thinning and stretching of the heart muscles resulting in enlargement of heart chambers that impairs the normal contraction and blood pumping [2]. DCMP presents with orthopnea, heart failure, breathlessness, impaired exercise tolerance, poor feeding, fatigue and sweating [3]. The prevalence of DCMP is estimated from 1:500 to 1:2500 in general population [4, 5]. In children, the incidence rate is about 0.57 per 100,000 population annually and is higher in boys than girls [6]. In children, the common causes of DCMP is idiopathic, neuromuscular disorders such as Becker and Duchenne dystrophies, nutritional deficiencies and inflammation [7]. Paediatric DCMP is observed to occur after influenza, parvo virus B19, coxsackie, herpes, Epstein Barr, adeno and human immunodeficiency viruses [7]. Furthermore, taurine, calcium, zinc and selenium depletion decrease the heart contractility and are implicated in DCMP [8].

Selenium and zinc, micronutrients found in red meat, grains, nuts and sea foods is an indispensable elements in human health [9]. Selenium in the form of selenocysteine and as the 21st amino acid is incorporated in the selenoproteins, modulating immunologic, cardiovascular and metabolic functions via anti-inflammatory, anti-cancer and anti-oxidant effects [10]. Also, selenium is crucial for sperm motility and thyroid function [11]. Glutathione peroxidases, iodothyronine deiodinases and thioredoxin reductases are anti-oxidant enzymes depending on selenium [12, 13]. Zinc is an important element in apoptosis and cellular membrane stability [14]. In addition, it is a necessary component of enzymes such as angiotensinogen converting enzyme and carbonic anhydrases that are regulators of acid-base balance and fluid homeostasis [15]. Zinc is a co-factor of different enzymes that contribute to function of anti-oxidant systems. It stabilizes cellular membrane and protects the cells against oxidative conditions. In addition, zinc inhibits pro-oxidant enzymes and decreases reactive oxygen species production in stress conditions [16–18].

Several studies have demonstrated that selenium deficiency may contribute to cardiovascular disorders such as Keshan disease, which is an endemic DCMP in China [19]. It is also indicated that zinc deficiency is culprit of cardiac cellular damage and decreased cardiac function [20, 21]. It is suggested that high selenium and zinc intake may reduce the risk of cardiovascular incidence and mortality [22]. Considering previous studies, little is known about the selenium and zinc intake in children

with DCMP, thus we aimed to explore the association of dietary intake of selenium and zinc with DCMP risk in children.

Methods and materials

Study population

In this case-control study, 45 patients within the age range of 2–17 years old who had been diagnosed with idiopathic DCMP for at least 6 months, were recruited from Rajaie cardiovascular, medical and research center during spring and summer of 2022 in Tehran, Iran. Physical exam, electrocardiogram (ECG), clinical history, echocardiography and chest X-ray had been used for diagnosis.

Inclusion criteria were individuals with signs and symptoms of heart failure such as low exercise tolerance, fatigue, edema and shortness of breath. Exclusion criteria were following: having renal failure, diabetes mellitus, malignancies, infectious disease, pregnancy, valvular, rheumatic, hypertensive and congenital heart diseases and also, life expectancy less than 6 months. Among 45 patients that were initially identified, 9 patients were excluded due to the high risk of mortality. Also, 72 controls were matched according to sex and age. The controls were randomly allocated patients admitted to other wards of the same hospital with no history of cardiovascular diseases, confirmed with echocardiography. It is important to mention that when the cases are selected from hospital, controls from hospital are preferred over community-based control selection. The protocol of this study was approved by Rajaie cardiovascular, medical and research center ethics committee (IR.RHC.REC.1401.016). All the parents / legal guardian of participants were informed about the study and signed the written informed consent form.

Dietary intake assessment

A reproducible and valid food frequency questionnaire (FFQ) [23–25] was used to collect dietary intake. A trained dietician collected the portion size and frequency of food items based on daily, weekly, monthly or yearly intake. The dietary intakes of participants were checked with their parents to reduce the recall bias. We used Nutritionist IV [26] to analyse the collected data and The United States Department of Agriculture (USDA) Food Composition Table (FCT) to calculate nutrients and energy contents.

Data collection

Socio-demographic and anthropometric information of the participants were collected by a trained interviewer. Body weight was measured to the nearest 100 g while standing on digital scales (Soehnle, Berlin, Germany). Height was calculated by a non-stretch portable meter to

Table 1 Baseline General Characteristics of Study Participants

	Case (n = 36)	Control (n = 72)	P value ¹
Sex (n) ¹	36	72	< 0.001
Male	15(41.6%)	58(80.5)	
Female	21(58.4)	14(19.5)	
Age (y) ²	9.83 ± 4.55	8.7 ± 1.54	0.157
Weight (kg) ²	35.38 ± 21.96	30.49 ± 9.47	0.208
BMI (kg/m ²) ²	16.9 ± 4.8	17.25 ± 3.58	0.702

Data are presented as frequency, percent and mean ± standard deviation

¹ Pearson chi-square test

² Independent t-test

Table 2 Dietary intakes of Study Participants

	Case (n = 36)	Control (n = 72)	P value
Protein (gr)	74.72 ± 34.43	115.22 ± 33.5	< 0.001
Carbohydrate (gr)	247.56 ± 88.89	569.94 ± 227.55	< 0.001
Total fiber (gr)	34.36 ± 18.41	8.4 ± 4.55	< 0.001
Fat (gr)	74.28 ± 30.6	115.48 ± 53.29	< 0.001
Cholesterol (mg)	264.86 ± 107.93	348.69 ± 145.98	0.003
SFA (gr)	23.23 ± 9.21	19.37 ± 34.19	0.372
Sodium (mg)	3836.71 ± 1624.36	5466.51 ± 3986.41	0.003
Potassium (mg)	3526.01 ± 1599.71	8577.74 ± 3938.85	< 0.001
Vitamin A.RE (mcg)	604.63 ± 362.26	3173.66 ± 2186.49	< 0.001
Vitamin C (mg)	169.23 ± 114.82	409.45 ± 369.28	< 0.001
Calcium (mg)	1294.89 ± 576.89	1342.24 ± 409.84	0.662
Iron (mg)	15.65 ± 9.44	47.39 ± 47.97	< 0.001
Vitamin D (mcg)	2.59 ± 1.71	16.21 ± 24.74	< 0.001
Vitamin E (mg)	11.23 ± 5.03	15.83 ± 14.25	0.016
Folate (mcg)	434.73 ± 181.89	621.89 ± 285.73	< 0.001
B12 (mcg)	5.51 ± 3.33	9.39 ± 10.24	0.004
Magnesium (mg)	316.09 ± 134.29	531.45 ± 211.95	< 0.001
Zinc (mg)	10.27 ± 4.76	13.44 ± 4.67	0.002
Selenium (mcg)	0.09 ± 0.04	0.13 ± 0.05	< 0.001

Independent t-test

Data are presented as mean ± standard deviation

the nearest 0.5 cm. Body mass index (BMI) was measured by dividing of weight in kilograms to square of height in meter.

Statistical analysis

After assessing the normality of the variable's distribution by Kolmogorov-Smirnov test, independent sample T-test was used to compare quantitative variables between the two groups, as Chi-square was also used for qualitative variables. The baseline characteristics were reported as mean ± standard deviation (SD) for quantitative variables, and number for qualitative variables. The association of selenium/zinc with the odds of cardiomyopathy was assessed by applying logistic regression. The analyses were adjusted for probable confounders, including age, sex, BMI, energy, fiber, Na and K. All analyses were performed using statistical package software for social

Table 3 Odds and 95% confidence interval for occurrence of cardiomyopathy in each tertile of selenium and zinc intake

	Tertiles of selenium intake			P value
	T1	T2	T3	
Selenium				
Model 1	1 (ref)	0.447 (0.172, 1.160)	0.144 (0.046, 0.455)	0.001
Model 2	1 (ref)	0.523 (0.185, 1.481)	0.180 (0.053, 0.611)	0.006
Model 3	1 (ref)	0.433 (0.137, 1.376)	0.198 (0.057, 0.693)	0.011
Zinc				
Model 1	1 (ref)	0.394 (0.150, 1.033)	0.179 (0.060, 0.534)	0.002
Model 2	1 (ref)	0.331 (0.111, 0.984/5)	0.134 (0.039, 0.465)	0.001
Model 3	1 (ref)	0.342 (0.108, 1.086)	0.127 (0.035, 0.466)	0.002

Model 1: Crude

Model 2: Adjustment for age, sex

Model 3: Additional adjustment for BMI, energy, fiber, Na, K, FBS, CRP

science (SPSS) 22.0 statistical software, and *P*-value less than 0.05 was considered statistically significant.

Results

Baseline characteristics

The mean ± SD for the age across case and control groups were 9.83 ± 4.55 and 8.7 ± 1.54 years, respectively. There was a significant difference in the distribution of sex between cases and controls (*p* < 0.001), with a higher proportion of males in the control group. However, no significant differences were observed in weight (*p* = 0.208) and BMI (*p* = 0.702) between the two groups (Table 1).

Dietary intakes

The dietary intakes of study participants across the case and control groups are presented in Table 2. Significant differences were found in the intake of protein, carbohydrate, total fiber, fat, cholesterol, sodium, potassium, vitamin A.RE, vitamin C, iron, vitamin D, vitamin E, folate, B12, magnesium, zinc, and selenium between cases and controls (*p* < 0.05 for all). Cases generally exhibited lower intakes of these nutrients compared to controls.

Odds ratios for cardiomyopathy

The odds ratio (ORs) and 95% confidence interval (CIs) for the occurrence of cardiomyopathy based on the tertiles of selenium and zinc intake are reported in Table 3. In the crude model, selenium and zinc were inversely associated with the lower odds of cardiomyopathy, with an OR of 0.144 and 0.179 for the highest tertile, respectively (*P* < 0.05 for trend). Furthermore, after adjusting for age, sex, BMI, energy, fiber, Na and K (in the fully adjusted model), in the highest versus lowest tertile of selenium and zinc, the lower odds of cardiomyopathy remained significant (OR = 0.198, 95% CI: 0.05–0.69; *P* value = 0.011 for trend and OR = 0.127, 95% CI: 0.03–0.46; *P* value = 0.002 for trend, respectively).

Discussion

The present case-control study demonstrated that lower intake of macronutrients and micronutrients such as selenium and zinc is associated with higher risk of DCMP in children, after fully adjusting of confounding factors such as energy, BMI, age, sex, fiber, Na and K.

In our study, dietary intake of macronutrients was significantly lower in cases than controls. Align with our finding Ocal et al. reported that children with malnutrition exhibit cardiovascular disorder including arrhythmia, sudden death, heart failure and dilated cardiomyopathy [27]. Also, gross examination of the myocardium in malnourished children showed a flabby, pale and thin-walled heart [28]. Nutritional interventions may improve the quality of life and myocardial function. Failure to thrive is one of the most important problems in children with cardiomyopathy. Adequate intake of macronutrients may improve cardiac function and also, specific micronutrients decrease the myocardial abnormalities that occur in cardiomyopathies and heart failure [29].

There is a vicious circle between malnutrition and DCMP. Poor nutritional status is a cause of DCMP and on the other hand, DCMP leads to malnutrition through metabolic disturbances, chronic inflammation and gastrointestinal malabsorption [30–32]. The inflammatory condition in most chronic diseases such as DCMP affects the metabolism and results in reduced cardiac muscle function and mass over time [33]. Different micronutrients deficiency may cause DCMP. Vema et al. reported a 15-month-old child with DCMP caused by hypocalcemia nutritional rickets that responded to vitamin D and calcium supplementation and systolic function normalized after 3 months [34].

Consistent with our study, Ripa et al. reported that primary or secondary zinc deficiency may result in DCMP and also, reduced plasma level of zinc is an important prognostic and diagnostic marker for DCMP [35]. In addition, Topuzoglu et al. demonstrated that patients with DCMP have lower plasma level of zinc compared with healthy controls [36]. Zinc is an important component of various enzymes such as superoxide dismutase. An impairment in superoxide dismutase function leads to reaction of superoxide anions with hydrogen peroxide and production of hydroxide radicals that induce cell damage. Zinc protects the cells against free radicals and thus decreases the cardiovascular disorders. In DCMP and consequently heart failure, activation of atrial natriuretic peptide (ANP) causes high urinary excretion of zinc, concluding to zinc deficiency and impaired cardiac performance [37]. On the other hand, Chou et al. did not find any association between patients with DCMP and control group [38]. The differences in reports may be due to sample size, dietary food intake and methodology.

Another micronutrient that is protective in cardiovascular diseases is selenium. Dasgupta et al. reported a 14 years old boy with severe malnutrition, selenium deficiency and heart failure that has been treated with selenium replacement and nutritional support and become completely asymptomatic after four weeks [33]. In line with our study, Khater et al. demonstrated that pediatric patients with DCMP have reduced plasma level of selenium and this element can prevent myocardial damage [39]. Frustaci et al. indicated that in patients with intestinal malabsorption, a reversible selenium and zinc DCMP may occur oxidative damages to cell membrane, increased cell autophagy and decreased anti-oxidant activity [40]. Furthermore, Basil et al. reported that selenium level is significantly lower in patients with DCMP in comparison with control group [41]. In contrast to our study, Cunha et al. investigated that there is no difference between selenium level in patients with DCMP and control group [42]. It may be due to different food pattern and sample size. Selenium is a crucial element in inflammation and immunity and improves antioxidant reserve and suppresses production of tumor necrosis factor alfa and interleukins. Selenium deficiency may also play a role in myocardial damage and recovery.

Current study has some strengths including the analysis of various macro and micronutrients and also adjusting the confounding factors to improve the reliability of the study. There are some limitations, due to case-control nature of the study we could not establish a causative relationship between selenium and zinc intake with DCMP and the possibility of recall bias is another issue to consider.

Conclusion

In conclusion, current study concluded that there is an inverse association between macronutrients, selenium and zinc intake with the risk of pediatric DCMP. Further studies are needed to evaluate the amount of selenium and zinc intake to prevent DCMP.

Abbreviations

DCMP	dilated cardiomyopathy
ECG	electrocardiogram
FFQ	food frequency questionnaire
USDA	the United States department of agriculture
FCT	food composition table
BMI	body mass index
SD	standard deviation
SPSS	statistical package software for social science
OR	odds ratio
CI	confidence interval
SFA	saturated fatty acid
RE	retinol equivalent

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Author contributions

Conceptualization, M.A.; Formal analysis, M.S and D.F.; Methodology, M.M, H.S and Y.R; Project administration, M.A and G.D; Writing – original draft, S.A and A.N.T; Writing – review & editing, G.D and S.A. All authors read and approved.

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Data availability

The datasets examined in the current study are available from the corresponding author on reasonable request.

Declarations**Ethics approval and consent to participate**

The protocol of this study was approved by Rajaie cardiovascular, medical and research center ethics committee (IR.RHC.REC.1401.016). All the parents / legal guardian of participants were informed about the study and signed the written informed consent form. All procedures performed in studies involving human participants adhered to the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Consent for publication

Not applicable.

Conflict of interest

The authors declare that they have no competing interests.

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