Oral Zinc Supplementation in Children with Dilated Cardiomyopathy: A Prospective Cohort Study in Assiut, Egypt

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Abstract:

Background: Zinc is an important micronutrient that affects the cardiovascular system by modulating oxidative stress. It is unclear whether zinc levels are affected in children with dilated cardiomyopathy (DCM).

Objectives: This research aims to detect the effect of oral zinc supplementation in pediatric patients with DCM who were admitted to the Cardiology Unit at Assiut University Children's Hospital (AUCH).

Methods: The present study was a prospective longitudinal cohort study in the Cardiology Unit, AUCH, and included 50 children diagnosed with impaired left ventricular systolic function due to DCM from September 2020 to February 2022. Patients were randomly divided into two groups: **Group A (Zinc supplemented group),** which received oral zinc supplementation in addition to inotropic and diuretic therapy, and **Group B (Non-zinc supplemented group),** which received only routine treatment, served as a control group. Patients were followed up thoroughly clinically and by echocardiography evaluation at the start of the study and after 6 months.

Results: The study included 50 children with DCM. According to New York Heart Association (NYHA) classification; 8%, 22%, 40%, and 30% had NYHA grade I, II, III, and IV respectively. After 6 months, the supplemented group had significantly higher LVFS and LVEF compared to controls, and the echocardiographic parameters showed significant improvement in LVFS (%)and LVEF (%) from baseline to after 6 months of receiving zinc supplementation, especially those with NYHA grade II-IV.

Conclusion: The current study provides evidence that oral zinc supplementation significantly benefits pediatric patients with DCM.

Keywords: Dilated Cardiomyopathy; NYHA classification; Oral Zinc Supplementation.

Introduction:

Cardiomyopathies are a group of heart diseases that directly affect the heart muscles and are unrelated to hypertension, congenital, valvular, or pericardial diseases. DCM is the most prevalent kind of cardiomyopathy (1). It typically presents with chronic systolic heart failure (HF), which is detected by echocardiography as impaired left ventricular function, shortening less than 28%, with left ventricular end-diastolic dimension Z-score>2, leading to arrhythmias and sudden death (2). Children under eighteen had an annual incidence of DCM of 0.57 cases per 100,000 (3).

Trace elements significantly influence myocardial metabolism. To sustain cyclic contractions and the regeneration of proteins and cells. HF is associated with neuro-hormonal activation, leading to increased levels of oxidative stress and inflammatory markers (4).

Zinc is an essential micronutrient that affects the cardiovascular system. Several possible pathophysiologic reasons for zinc shortage in HF include reduced absorption, hyperinflammatory conditions, compromised

micronutrient consumption, and hyperzincuria from HF medicines. One potential cause of DCM could be zinc deficiency (5-7).

Numerous observational studies of patients with HF have recorded plasma zinc levels. Serum zinc levels are low, especially in studies with idiopathic DCM (8-10).

The average daily amount of intake that is adequate to meet the nutrient requirements of almost all (97–98%) healthy individuals is known as the recommended dietary allowance (RDA). When there is insufficient information from scientific research to establish an RDA, the level known as appropriate intake (AI) is established as follows: infants (AI), 2 mg daily (mg/day) for 0 to 6 months, and 3 mg/day for 7 to 12 months. Children (RDA): 3 mg/day for ages 1 to 3, 5 mg/day for ages 4 to 8, 8 mg/day for ages 9 to 13, and 5 to 20 mg/day for supplementation (11).

A small but growing body of research suggests oral zinc supplementation may help treat DCM (12-14). However, further evaluation of the impact on the outcome is warranted. Thus, the main objective of the current study is to determine the impact of oral zinc supplementation in pediatric DCM patients.

Patients and Methods:

This study was a hospital-based longitudinal cohort study. The study was approved by the regional ethics committee at Assiut University (IRB No 17101425). Informed written consent was obtained from all participants' parents before enrolling in the current study.

(A) Patients:

Fifty children aged 1–18 years diagnosed with DCM and attending the Pediatric Cardiology Unit at AUCH from the first of September 2020 to the end of February 2022 were enrolled in the current study. Infants (aged less than one year), patients with impaired left ventricular systolic function due to other causes like congenital or acquired heart diseases, and those who refused to participate in the study were excluded.

Patients were randomly "based on simple randomization technique by computer-generated sequence" divided into two groups:

- **Group A (zinc-supplemented group):**

Patients received oral zinc supplementation according to RDA for age using sulfozinc syrup (10mg /5ml and 20mg/5ml) and inotropic and diuretic therapy.

- **Group B (Non-zinc supplemented group):**

Patients receiving only routine treatment serve as controls.

Patients were followed up thoroughly clinically and by echocardiography evaluation at the start of the study and after 6 months of zinc supplementation.

(B) Data collection:

Eligible participants were subjected to full history taking, including name, age, sex, NYHA functional classification for grading HF (15), and anthropometric measurements [height in cm, weight in kg, and body mass index (kg/m^2)].

A pediatric experienced cardiologist had performed echocardiography screening with a Philips Envisr C ultrasound machine, according to the guidelines of the American Society of Echocardiography (16), focusing on follow-up of left ventricle end-diastolic dimension Z-score, left ventricle fractional shortening, and ejection fraction.

(C) Statistical Analysis:

Version 22 of SPSS (Statistical Package for the Social Sciences; SPSS Inc., Chicago, IL, USA) was used for all statistical computations. The data were provided as numbers (percentages) and compared using the Chi-square ($\chi 2$) or Fisher Exact test, or statistically described as mean±standard deviation (±SD), median, and range, and compared using the Mann-Whitney U test. Significant P-value set at 0.05.

Results

Demographic data of the studied patients

The study included 50 patients with DCM (25 received zinc supplementation in addition to the routine treatment for cardiomyopathy), and 25 received only the

routine treatment. The median age of the studied participants was 9 years (range: 1–14 years), with a male-to-female ratio of 1.8:1. Other data were presented in **Table 1**. Both studied groups were comparable regarding the baseline data (age, sex, and BMI), with no significant difference between them (P > 0.05 for all).

According to NYHA functional classification, 8%, 22%, 40%, and 30% had NYHA grade I, II, III, and IV respectively. With no significant difference between the studied groups (P=0.703)

(Table 1).

Table (1): Demographic and clinical data of both studied groups

Demographic data	Total cases (n=50)	Zinc-supplemented group (Group A, n=25)	Non-zinc supplemented group (Group B, n=25)	P value
Age (year)	9 (1–14)	9 (1–14)	10 (2–14)	0.458
Sex				0.554
• Male	32 (64.0%)	18 (72.0%)	14 (56.0%)	
• Female	18 (36.0%)	7 (28.0%)	11 (44.0%)	
BMI (kg/m^2)	15.5 (12.2–24.9)	15.5 (12.4–18.0)	15.4 (12.2–24.9)	0.554
NYHA classification				0.703
• Grade 1	4 (8.0%)	2 (8.0%)	2 (8.0%)	
• Grade 2	11 (22.0%)	6 (24.0%)	5 (20.0%)	
• Grade 3	20 (40.0%)	8 (32.0%)	12 (48.0%)	
• Grade 4	15 (30.0%)	9 (36.0%)	6 (24.0%)	

Data are presented as median (range) or number (percentage). Significance defined by p<0.05

Echocardiographic findings between the groups

At baseline, all echocardiographic findings regarding LVEDD, LVFS, and LVEF were comparable between both groups with no significant difference (P=0.153, 0.187, and 0.054, respectively). After six months, Group A (zinc-supplemented group) had significantly higher LVFS and LVEF (%) than Group B(non-zinc-supplemented group) (P < 0.05) **(Table 2)**.

Table (2) Comparison of echocardiographic findings between both studied groups at the start of the study and after 6 months (n=50)

Echocardiographic finding	Zinc-supplemented group (Group A, n=25)	Non-zinc supplemented group (Group B, n=25)	P value
At the start of the study			
• LVEDD (%)	58 (41–70)	54.7 (36–68)	0.153
• LVFS (%)	20 (10 – 24)	15 (10 – 32)	0.187
• LVEF (%)	40 (22 – 48)	35 (20 – 57)	0.054
After 6 months			
• LVEDD (%)	58 (40 – 70)	58 (34 – 69)	0.676
• LV FS (%)	21 (12 – 30)	16 (9 – 40)	0.001
• LVEF (%)	42 (28 – 57)	31 (19 – 63)	<0.001

LVEDD: left ventricular end-diastolic diameter; **LVFS:** left ventricular fractional shortening; **LVEF:** left ventricular ejection fraction. Data are presented as median (range). Significance defined by p < 0.05.

Echocardiographic findings among patients who received zinc supplementation

Among patients who received zinc supplementation, the echocardiographic parameters showed significant improvement in LVFS (%)and LVEF (%) from baseline to after six months of zinc supplementation (P=0.005 and 0.001), respectively. While LVEDD (%) shows no significant difference from baseline to after six months of receiving zinc supplementation (P=0.527), **Table (3)**.

Table (3) Comparison of echocardiographic findings from baseline to after 6 months of zinc supplementation in Group A (zinc supplemented group) (n=25).

Echocardiographic finding	At baseline	After 6 months of zinc supplementation	P value
• LVEDD (%)	58 (41 – 70)	58 (40 – 70)	0.527
• LVFS (%)	20 (10 – 24)	21 (12 – 30)	**0.005**
• LVEF (%)	40 (22 – 48)	42 (28 – 57)	**0.001**

Data are presented as median (range). Significance defined by $p < 0.05$.

Echocardiographic findings in Group A (zinc-supplemented group) according to the NYHA classification

No significant improvement was observed for patients with NYHA grade I from baseline to after six months of zinc supplementation among patients with NYHA grade 1 (P > 0.05).

For patients with NYHA grade II, there was a significant reduction in LVEDD (%) (P=0.026), a significant increase in LV FS (%) (P=0.023), and a significant increase in LV EF (%) (P=0.023).

For patients with NYHA grade III, there was a significant increase in LV-FS (%) (P=0.011) and a significant increase in LV-EF (%) (P=0.017), while LVEDD (%) was comparable from baseline to after 6 months of zinc supplementation (P=0.122).

For patients with NYHA grade 4, LVEDD (%) shows a significant increase in length (P=0.011), and LV-EF (%) shows a significant increase (P=0.045) from baseline to after the follow-up period, while LV-FS (%) was comparable from baseline to after 6 months of zinc supplementation (P=0.633), **Table (4)**.

Table (4) Comparison of echocardiographic findings in Group A (zinc-supplemented group) according to the NYHA classification from baseline to after 6 months of zinc supplementation (n=25).

Echocardiographic finding	At baseline	After 6 months of zinc supplementation	P value
NYHA Grade I, n=2			
• LVEDD (%)	49.2 (46.6 – 51.7)	46.1 (41.1 – 51.0)	0.180
• LVFS (%)	11.5 (10 – 13)	20 (17 – 23)	0.180
• LVEF (%)	25 (22 – 28)	38 (29 – 47)	0.180
NYHA Grade II, n=6			
• LVEDD (%)	67 (44.9 – 68.0)	66.3 (41.5 – 67.6)	**0.026**
• LV FS (%)	20 (17 – 24)	21 (18 – 30)	**0.023**
• LVEF (%)	40 (38 – 48)	42 (40 – 57)	**0.023**
NYHA Grade III, n=8			
• LVEDD (%)	60.9 (41 – 70)	57.2 (40 – 62.1)	0.122
• LVFS (%)	18.5 (14 – 21)	23 (20 – 26)	**0.011**

• LVEF (%)	37.5 (31 – 41)	44 (39 – 50)	**0.017**
NYHA Grade IV, n=9			
• LVEDD (%)	58 (44.0 – 68.9)	58 (45 – 70.1)	**0.011**
• LV FS (%)	20 (14 – 24)	18 (12 – 25)	0.633
• LVEF (%)	40 (30 – 44)	42 (28 – 46)	**0.045**

Data are presented as median (range). Significance defined by $p < 0.05$.

Discussion

Heart failure can result from DCM, an uncommon yet debilitating cardiac condition (17). Antioxidants are crucial for preserving cellular function. It could defend against coronary artery disease and cardiomyopathy (18). Cardiomyocyte apoptosis is linked to zinc deficiency (19). Reduced zinc levels have been linked to reversible cardiomyopathy (7, 20). Even so, some research indicates that HF is linked to decreased zinc concentrations (20). The present study aimed to determine the impact of oral zinc supplementation in pediatric DCM patients.

The study included 50 patients with DCM, with a median age of 9 years (range: 1–14 years), with slight male sex predominance. Consistent with this study, previous research on the sex differences in myocarditis patients found that males were somewhat more likely than females to have myocarditis (sex ratio: 1:1.5 to 1:1.7) (21, 22) and a higher chance of the disease progressing (23).

The study participants were divided into two groups: 25 patients who received zinc supplementation in addition to the routine treatment for cardiomyopathy, and 25 patients who received the routine treatment only served as controls. Currently, the most commonly used scale for assessing HF severity in childhood and adolescence is the NYHA Functional Classification (FC) (24). Among the studied participants; 8%, 22%, 40%, and 30% had NYHA grade I, II, III, and IV respectively. Both studied groups were comparable in terms of NYHA classification.

By comparing the echocardiographic parameters between both groups, we observed that at baseline, all echocardiographic findings regarding LVEDD, LVFS, and LVEF were comparable, with no significant difference between them. After six months of zinc supplementation, Group A (zinc-supplemented group) had significantly higher LVFS and LVEF than Group B (non-zinc-supplemented group). Additionally, Group A (zinc-supplemented group) showed significant improvement in LVFS (%)and LVEF (%) from baseline to after six months of zinc supplementation. This indicates the beneficial role of zinc in improving the cardiac diameter and function among children with DCM.

Numerous investigations revealed a link between zinc deficiency and HF, including in patients with DCM (25, 26). Patients with congestive heart failure (CHF) experienced improvements in their left ventricular sizes, left ventricular ejection fraction, and quality of life after receiving several micronutrient supplements for six months (27).

A recent study conducted in Egypt aimed to determine the impact of zinc supplements on the diabetic left ventricle (LV) in children and adolescents with type 1 diabetes. After six months, the authors found that patients who received zinc had considerably lower serum levels of IL-6 than those who did not. Additionally, this study demonstrated a significant improvement in the diastolic function and E/A ratio in the diabetic individuals who received oral zinc supplements (28).

Low serum zinc levels were linked to higher rates of diabetes, coronary artery disease, and other related risk factors, including hypertension, hypertriglyceridemia, and insulin resistance, according to a study done in North Indian rural and urban populations (29).

Patients with HF had significantly decreased serum zinc concentrations

compared to adult patients with DCM (30,31). Another study by Topuzoglu and colleagues on 54 adult DCM patients, with LVEF of 35% and NYHA clinical class III-IV, compared to 20 healthy controls. According to the authors, patients with HF had significantly lower serum zinc concentrations (32).

Arroyo and colleagues' study on 40 African-American patients, more than 70% of patients with HF, NYHA symptomatic class III-IV, and LVEF 35% showed evidence of zinc insufficiency (33).

In a study by Kosar and colleagues, 54 HF patients with NYHA class II-IV and 30 age- and sex-matched healthy controls were compared. The HF patients' mean serum zinc level was significantly lower (20).

A growing body of research indicates that low zinc levels are linked to the development of cardiovascular diseases. The relationship between zinc levels and different CVDs needs to be established.

Study limitations:

We couldn't estimate the serum zinc level among the studied participants due to a lack of adequate financial support, and unfortunately, this test has a high cost.

Conclusion

After 6 months of zinc supplementation, DCM patients with NYHA grade II-IV show significant cardiac diameter and function improvement. Thus, the current study provides evidence that oral Zinc supplementation significantly benefits pediatric patients with DCM.

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