Cardiology in the Young

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Low pre-albumin but not thiamine predicts cognitive deficits in adolescents post-Fontan and healthy controls

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Original Article

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Abstract

Background: Low pre-albumin, body mass index, and thiamine levels have been associated with poor nutritional status and cognitive/memory deficits in adult heart failure patients. However, the relationship of these nutritional/dietary intake biomarkers to cognition has not been assessed in adolescents post-Fontan procedure and healthy controls. *Methods:* This is a cross-sectional study. Adolescents (14–21 years of age) post-Fontan completion were recruited from paediatric cardiology clinics and controls from the community. The Montreal Cognitive Assessment was administered (normal ≥ 26), and blood draw (thiamine [normal 70–110 nmol/L] and pre-albumin levels [adolescent normal 23–45 mg/dL]) and the Thiamine Food Frequency Questionnaire were completed by all participants. *Results:* Seventy subjects, 40 post-Fontan (mean age 16 ± 1.6, female 51%, Hispanic 44%, hypoplastic left heart syndrome 26%) and 30 controls (mean age 16.8 ± 1.9, female 52%, Hispanic 66%), were participated. Post-Fontan group had lower median total cognitive scores (23 versus 29, $p < 0.001$), pre-albumin levels (23 versus 27, $p = 0.013$), and body mass index (20 versus 24, $p = 0.027$) than controls. Post-Fontan group had higher thiamine levels than controls (127 versus 103, $p = 0.033$). Lower pre-albumin levels (< 23) and underweight body mass index were associated with abnormal total cognitive scores ($p = 0.030$). Low pre-albumin level ($p = .038$) was an independent predictor of worse cognition. *Conclusion:* Lower pre-albumin was an independent predictor for worse cognition in adolescents post-Fontan. Lower pre-albumin levels may reflect chronic liver changes or protein-losing enteropathy seen in Fontan physiology. These findings highlight the possibility for nutrition-induced cognitive changes.

Single-ventricle CHD is the most critical subtype of CHD that requires multi-staged palliative surgeries with the culmination being the Fontan procedure.[1] Although these surgeries are essential for long-term survival, these children face multiple comorbidities associated with chronic Fontan physiology (e.g., Fontan-associated liver disease and protein-losing enteropathy).[2] Two common concerns in this population have been the ability to gain weight pre-Fontan and cognitive deficits. Approximately, 25% of children with single-ventricle CHD have known growth and nutritional deficits.[3] Factors contributing to these deficits include a high metabolic demand, inadequate caloric intake, altered intestinal pathology, and genetic and extracardiac abnormalities.[4–6]

The cognitive deficits often become more apparent in adolescence where higher-level executive functioning skills are required. The aetiology of these cognitive deficits is unclear but presumed to be multifactorial (e.g., brain maturation, cyanosis, surgical, and perioperative factors).[2,7] However, it is unknown if nutritional status (e.g., body mass index, pre-albumin, and thiamine) contributes to cognitive deficits in adolescents with single-ventricle CHD.

Thiamine, also known as vitamin B_1, is a water-soluble vitamin found in meat, wholegrains, fish, and nuts and is necessary for the normal functioning of the nervous system. Symptoms of thiamine deficiency include fatigue, memory loss, depression, nausea, cardiomyopathy/heart failure ("wet beriberi"), and muscle cramps. Humans are dependent on dietary intake to fulfil their thiamine requirements as very little thiamine is stored in the body, and depletion can occur within 14 days. Thiamine deficiency has been reported in adult heart failure and was associated with loop diuretic use[8] and memory deficits in other clinical conditions.[9,10] Thiamine deficiency was also noted in 27% of young children in heart failure on loop diuretics with a ventricular septal defect both before and after surgical closure.[11] Although loop diuretics enhance the excretion of thiamine and may lead to its deficiency, low levels of thiamine can develop secondary to inadequate intake from the diet.[8,12,13]

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Pre-albumin is known to be a biomarker of protein nutritional status (e.g., malnutrition) with lower levels being associated with reduced survival and higher readmission rates in adult heart failure.[14,15] There continues to be variability related to body mass index reported in the Fontan population with many identified as under to normal weight and felt to be associated with decreased intestinal perfusion and absorption of nutrients contributing to a cardiac cachexia clinical picture.[1,16–18] Conversely, other studies have shown overweight and obesity secondary to decrease functional status related to worsening clinical condition or Fontan failure.[19–21]

The relationship of these nutritional biomarkers to cognitive function has not been assessed in adolescents with single-ventricle CHD post-Fontan procedure. The identification and treatment of dietary deficiencies could potentially enhance cognitive performance and ultimately self-care.[13] Therefore, the purpose of this study was to evaluate nutritional status (pre-albumin, body mass index, and thiamine) in adolescents with single-ventricle CHD post-Fontan and healthy controls to identify possible associations with impairment of cognitive function.

Materials and methods

Study design, sample, and setting

In this cross-sectional, comparative pilot study, 70 adolescents (40 single-ventricle CHD and 30 controls), aged 14 to 21 years, were recruited via flyers or provider referral from paediatric cardiology clinics in Southern California and healthy controls from the local community. The single-ventricle heart disease group included adolescents who had undergone surgical palliation with Fontan completion and were excluded for severe developmental delay that precluded the ability for self-report (e.g., cerebral palsy). Controls were excluded for any chronic medical or psychiatric condition.

Data collection

After Institutional Review Board approval from the University of California, Los Angeles (#16-000433), parental permission and assent were obtained for participants under the age of 18 years, and informed consent was obtained from participants aged 18 years and over. All participants completed a demographic form (e.g., age, gender, and ethnicity), food frequency questionnaire, the Montreal Cognitive Assessment, and a blood sample with laboratory analysis to assess pre-albumin and thiamine levels. All blood samples and laboratory analyses were performed at the same outpatient centre at UCLA. Clinical information was extracted from the medical records (e.g., type of single ventricle and Fontan procedure, number of surgeries, current oxygen saturation, height, weight, body mass index, and medications [including over-the-counter drugs and multivitamins]).

Measurements

Montreal Cognitive Assessment

The Montreal Cognitive Assessment is an administered screener used to measure multiple domains of cognitive function, such as visuospatial, attention/concentration, executive function, language, delayed memory recall, and naming.[22] The visuospatial and executive function tasks are written items (e.g., three-dimensional cube, Watson Clock Drawing Task, and alternating Trail Making Task Part B), and the remaining are scored based on verbal response.[22] The total score ranges from 0 to 30, and a score < 26 is considered abnormal. The Montreal Cognitive Assessment has been validated in adolescents both with and without CHD and has a Cronbach's alpha of 0.8.[23]

Body mass index

All participants' height and weight were obtained in order to calculate their body mass index value. Body mass index was assessed based on the weight-for-age and gender growth charts.[24] (Center for Disease Control and Prevention [CDCP], 2017).

Pre-albumin and thiamine laboratory tests

Venous blood was collected at the same lab for all participants and assayed. The adolescent normal values for thiamine (normal 70–110 nmol/L) and pre-albumin levels (normal 23–45 mg/dL)] were used based on the UCLA outpatient laboratory reference ranges. Participants were notified if levels were below the normal range.

Thiamine Food Frequency Questionnaire

The Thiamine Food Frequency Questionnaire was developed by the investigator due to a lack of instruments available that assess the intake of foods rich in thiamine and fast-food consumption. This was developed based on the validated Food Frequency Index which captures dietary patterns and not portions consumed, a Likert scale format, and relied on a 7–30-day recall period[25]. Since thiamine has a short half-life, the questionnaire was based on foods consumed in a given week. A seven-item, questionnaire was used to assess how often *vegetables and fruits*, *breads and grains*, *meats*, *nuts and seeds*, *dairy*, *beans and legumes*, and *fast foods* were consumed in a given week. Response options were *never, once a week, 1–3 times a week, 4–5 times a week, once a day, or twice or more times a day* with corresponding scores of 0–5. A single-item question was asked regarding intake of multivitamin use. The Thiamine Food Frequency Questionnaire was pilot-tested in three adolescents to assess face validity and a nutritional expert for content validity. Total scores ranged from 0 to 36 with higher scores indicating increased dietary intake of thiamine.

Statistical analyses

Sample characteristics are presented as means with standard deviations or medians with interquartile ranges for continuous variables and Chi-square for categorical variables. The variables were examined for normality (thiamine and pre-albumin normally distributed, and cognitive scores not normally distributed) by the Shapiro–Wilks tests. Thus, non-parametric statistics (Mann–Whitney U and Kruskal–Wallis tests) were used to assess group differences (single-ventricle CHD versus control), Montreal Cognitive Assessment group (low versus high scores), compared to body mass index (Center for Disease Control and Prevention guidelines – underweight, normal, and overweight), thiamine, and pre-albumin levels. Spearman's rho correlation coefficients were used to assess variables associated with total Montreal Cognitive Assessment scores. Only variables with significant correlations ($p = 0.05$) were entered into the multivariate analysis using linear regression to assess predictors of cognitive scores. All analyses were conducted with the Statistical Package for the Social Sciences version 23.0 (IBM; Somers, NY) with a significance set at a p-value < 0.05.

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Table 1. Demographic, cognitive, and laboratory results between groups (n = 70).

Variable	SVHD (n = 40)	Controls (n = 30)	p-Value
Age (mean SD)	16 (1.6)	16.8 (1.9)	0.186
Gender (male) %	20 (51%)	15 (52%)	0.497
Ethnicity			0.152
Hispanic	17 (44%)	19 (66%)	
White	14 (36%)	5 (17%)	
Other	8 (20%)	5 (17%)	
Body mass index (mg/kg) (median)	20 (18, 23)	23 (20, 25)	0.005
Underweight	14 (35%)	2 (7%)	
Normal	20 (50%)	20 (66%)	
Overweight/obese	6 (15%)	8 (27%)	
Single ventricle type (right) %	23 (58%)	N/A	N/A
Diagnosis n (%)		N/A	N/A
Hypoplastic left heart syndrome	15 (38%)		N/A
Double-outlet right ventricle	6 (15%)		N/A
Unbalanced atrioventricular canal	6 (15%)		N/A
Tricuspid atresia	3 (8%)		N/A
Other	10 (25%)		N/A
Number of surgeries (median)	3 (2–4 range)	N/A	N/A
Oxygen saturation<93%	7 (28%)	N/A	N/A
Number of daily medications	3 (0–6 range)	N/A	N/A
Diuretic use (yes)	5 (13%)		N/A
Protein-losing enteropathy (yes)	4 (10%)	N/A	N/A
Multi-vitamin supplement (yes)	31 (78%)	3 (10%)	0.001
MoCA total (median [IQR])	23 (21, 25)	29 (26, 30)	0.000
Visuospatial/executive function	4 (3, 5)	5 (5, 5)	0.000
Attention	4 (3, 5)	6 (5.5, 6)	0.000
Language	2 (1, 3)	3 (3, 3)	0.000
Delayed recall memory	2 (1, 3)	3 (2, 4.5)	0.005
Naming	3 (3, 3)	3 (3, 3)	0.129
Abstraction	2 (1, 2)	2 (2, 2)	0.001
Pre-albumin	23 (21, 27)	27 (24, 30)	0.013

MoCA = Montreal Cognitive Assessment; N/A= not applicable; TFFQ = Thiamine Food Frequency Questionnaire; SD = standard deviation; SVHD = single-ventricle heart disease.
*Mann–Whitney U-test.

Results

Sample characteristics between groups

A total of 70 adolescents, 40 single-ventricle CHD (mean age 16 ± 1.6, female 51%, Hispanic 44%, hypoplastic left heart syndrome 26%) and 30 controls (mean age 16.8 ± 1.9, female 52%, Hispanic 66%), were studied. Five were excluded from the analysis secondary to lab processing errors or inability to obtain blood samples after the second venipuncture attempt. No significant differences in age, gender, or ethnicity appeared between groups. Body mass index was higher in the controls compared to single-ventricle CHD group (24 versus 20; p = 0.005) (Table 1).

Thiamine, pre-albumin, body mass index, dietary intake, and cognitive scores between groups

Single-ventricle CHD group had lower median total Montreal Cognitive Assessment scores (23 versus 29, p < 0.001) including subscales except naming and pre-albumin levels (23 versus 27, p = 0.013) than controls. Single-ventricle CHD group had higher thiamine levels than controls (127 versus 103, p = 0.033) and a higher intake of multivitamins (Table 1). A comparison of dietary intake between groups using the Thiamine Food Frequency Questionnaire showed no statistically significant difference in individual food categories except for a higher intake of fast food in the control group (p = 0.049).

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Table 2. Cognitive scores associated with thiamine, pre-albumin, and BMI.

Variable	MoCA<26 (abnormal) (n = 45)	MoCA≥26 (normal) (n = 25)	p-Value
	Median (IQR) or n (%)		
Thiamine level (nmol/L)	122 (93, 144)	103 (30)	0.359
Pre-albumin Level (mg/dL)	23 (21, 27)	27 (3.5)	0.030
BMI (mg/kg) (median)	20 (18, 24)	24 (20, 25)	0.043
Underweight n (%)	16 (36%)	2 (8%)	0.039
Normal n (%)	26 (58%)	21 (84%)	0.050
Overweight n (%)	3 (7%)	2 (8%)	0.244

BMI = body mass index.
Mann–Whitney U-test and Kruskal–Wallis test.

Cognitive scores associated with thiamine, pre-albumin, and body mass index

Lower pre-albumin levels (< 23) and underweight body mass index were associated with abnormal total Montreal Cognitive Assessment scores ($p = 0.030$) in both single-ventricle CHD and control groups (Table 2). There were no significant differences between groups with low pre-albumin levels and cognitive scores ($p = 0.07$). Pre-albumin ($r = .262^*$; $p = .037$) and body mass index ($r = .264^*$; $p = .030$) but not thiamine ($r = -0.009$, $p = .256$) were correlated with Montreal Cognitive Assessment scores. Of note, pre-albumin was correlated with visuospatial/executive function ($r = .263^*$; $p = .036$) and attention ($r = .261^*$; $p = .025$) subscales of the Montreal Cognitive Assessment. Lastly, low pre-albumin level was the only independent predictor of worse cognition ($\beta = 0.260$, $R^2 = 0.67$, adjusted $R^2 = 0.052$, $F = 4.480$; $p = 0.038$).

Discussion

Thiamine levels in adolescence with and without single-ventricle heart disease

Our study findings identified that thiamine was not deficient in adolescents with single-ventricle CHD and were higher than in controls. Of interest, the majority of the single-ventricle heart disease group were taking a daily multivitamin (usually 50–100 mg of thiamine) compared to only a few in the control group. Dietary intake of foods high in thiamine was not different between groups except the control group that had a higher intake of fast foods than the single-ventricle CHD group. The general adolescent diet is often high in processed or ultra-processed foods (e.g., fast food), which can lower micronutrient intake, in particular thiamine, and has been shown to impact cognitive function in adolescents.[26] This may be reflective of the lower thiamine levels in the control group.

Vigilant parenting behaviours and few adolescents on diuretic therapy may explain the higher thiamine levels seen in the single-ventricle CHD group compared to controls. Parents of children with severe CHD tend to be very observant and have learned to closely monitor dietary intake and weight gain to promote their child's well-being.[27–29] Consequently, these vigilant behaviours may continue into adolescence and young adulthood and be manifested by daily multivitamin intake and decreased fast-food consumption. Furthermore, only a few adolescents were on diuretic therapy greater than 10 years out from the Fontan procedure. Studies in adult heart failure acknowledge the excretory influence on thiamine levels which maintained on high-dose diuretics.[8] Despite higher thiamine levels in the single-ventricle CHD group, cognitive scores were worse compared to controls indicating other factors affecting cognitive function. In addition, there was no difference between groups with low pre-albumin and cognitive scores indicating the possibility for nutrition-induced changes.

Body mass index and pre-albumin related to cognition

Our findings identified lower body mass index and pre-albumin levels to be associated with lower cognitive scores. Unfortunately, there are no studies evaluating the association between cognitive scores with body mass index and/or pre-albumin levels in adolescents with CHD or specifically single-ventricle CHD. These finding may reflect their clinical condition or disease severity. Low serum albumin levels related to enteric protein loss are not uncommon post-Fontan.[30,31] Prolonged Fontan physiology results in decreased cardiac output and increased central venous pressures, which changes mesenteric blood flow. High central venous pressures post-Fontan can alter protein absorption and compromise weight gain (not fluid secondary to ascites or peripheral oedema) in patients with protein-losing enteropathy. Albumin and pre-albumin can also be low in patients with an acute or chronic inflammatory illness or conditions. A low-flow state of chronic heart failure results in the stimulation of the inflammatory system, which appears to be similar post-Fontan.[32] Studies have shown that 30% of patients post-Fontan with protein-losing enteropathy have elevated inflammatory biomarkers (e.g., C-reactive protein) in the presence of low albumin.[32] Despite only four adolescents in our study with documented protein-losing enteropathy, low normal pre-albumin levels may be inherent in the condition and reflective in our findings.

Poor linear growth in the face of high caloric intake is well documented in children pre-Fontan[33] with some identifying an association with neurodevelopment and cognitive deficits.[4] Our study identified executive function, visuospatial, memory, attention, and concentration deficits that are congruent with many studies assessing neurocognitive outcomes in this population.[2,34,35] However, these studies did not examine specific nutritional biomarkers or body mass index related to cognitive outcomes. Although the literature on low versus high body mass index and cognitive performance in children remains controversial, our

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findings are plausible based on established links between nutritional deficiencies and compromised cognitive development.[36,37] Sarcopenia associated with lean muscle mass deficits as in cardiac cachexia has been reported in Fontan patients and felt to be similar to patients with advanced heart failure from acquired heart disease.[38,39] Conversely, increased body mass index in adult Fontan patients has been associated with symptomatic heart failure or Fontan failure.[20,21] Thus, our Fontan population is younger in age with few on diuretics or protein-losing enteropathy, which may reflect a more stable chronic condition. Future studies are needed to confirm these findings and investigate other potential contributing factors such as reduced cerebral blood flow associated with lower cardiac output with ageing and its effect on cognition. Furthermore, future studies are needed to assess if an increase in protein intake (preferably in liquid form for easier absorption) could improve weight gain and cognitive performance for selected patients.

Limitations

Our study should be viewed in light of some limitations. The sample size was relatively small which limits our ability to perform additional analyses based on diuretic and multivitamin use. We also did not anticipate the number in the single-ventricle CHD group who were taking daily multivitamins and a healthier diet and not taking diuretics. Furthermore, using the Thiamine Food Frequency Questionnaire which was adapted from a known validated instrument to assess dietary intake, we modified the instrument for brevity to assess dietary consumption of foods high in thiamine, and this altered the validity of the instrument. Finally, the cross-sectional nature of the study limits our ability to establish any causal relationship.

Conclusion

Lower pre-albumin was an independent predictor for worse cognition in adolescents with single-ventricle heart disease and controls. Lower pre-albumin levels may reflect chronic liver changes or protein-losing enteropathy seen in Fontan physiology. These findings highlight the possibility for nutrition-induced cognitive changes. Improved nutritional status, in particular protein intake, in adolescents with single-ventricle CHD should be assessed as a potential treatment to improve cognitive performance.

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Competing interests. None.

Ethical standard. This research did not involve human or animal experimentation. Approval was obtained from the institutional review boards.

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