The effect of malnutrition on T3 levels in pediatric patients undergoing congenital heart surgery

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Abstract

***Objective*: To define the effect of malnutrition and other factors such as age, the type of congenital heart defects and hemodynamics on T3 levels in pediatric patients with congenital heart anomalies before corrective surgery.**

***Design*: prospective cross sectional study.**

***Setting*: 13-bed Pediatric Cardiac Intensive Care Unit (PCICU) at the National Cardiovascular Center Harapan Kita, Jakarta, Indonesia.**

Patients and participants: Children between 0 and 2 years of age undergoing congenital heart surgery on cardiopulmonary bypass with an Aristotle score of 6 and above.

***Interventions*: No intervention.**

***Measurements*: We prospectively enrolled over a 6-month period all patients less than 2 years of age undergoing congenital heart surgery. Baseline levels of TT3, FT3, TT4, FT4 and TSH were measured before surgery. The nutritional status was estimated from standard anthropometric measurements. The thyroid hormone levels were then correlated using unpaired T-test and Mann Whitney test.**

***Result*: Out of 43 patients enrolled, 60.4% patients presented with moderate to severe malnutrition. Mean baseline FT3 levels were significantly reduced in severely malnourished patients compared to those in the well-nourished group (FT3: 4.9±0.7 vs. 3.5±0.3 pg/ml, p=0.04). There were no significant differrences of TT3, TT4, FT4 and TSH between groups. Sex, age, the presence of cyanosis and unrestrictive pulmonary blood flow before surgery did not show any significant differences of thyroid hormone levels between groups.**

***Conclusions*: Severe malnutrition has a significant impact on FT3 levels in cardiac patients before surgery that make this group of patients probably more prone to an increased morbidity associated with a low T3 state (i.e. SES) after surgery.**

Key words: Cardiopulmonary bypass, congenital heart surgery, thyroid hormones, euthyroid sick syndrome, malnutrition.

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Introduction

A marked decline in thyroid hormone levels after cardiac surgery using cardiopulmonary bypass (CPB) has been well described as sick euthyroid syndrome (SES). (1) This transient decrease of thyroid hormones is only present for a temporary period reaching its maximum usually between 12 and 48 hours after CPB and recovering to normal within the following 5 to 7 days postoperatively. The SES is related to a significant deterioration of cardiac ouput due to left ventricular dysfunction and increased vascular resistance as well as impaired urine output and ventilatory drives. (2) Especially the group of neonates and children below 6 months of age with prolonged cardiopulmonary bypass and deep hypothermic circulatory arrest had been identified as patients at risk to have more severe SES. (3)

In Indonesia, our patients' population usually present different from those patients in developed countries; most of our patients present somewhat late and therefore with long lasting hemodynamic compromise of the congenital heart defects. Typically they suffer from prolonged heart failure, pulmonary hypertension, cyanosis, recurrent infections and especially malnutrition before corrective surgery. Malnourishment alone is known to have significant impact on T3 levels due to a decreased stimulation of leptin on the TRH receptor in the paraventricular nucleus of hypothalamus. (4) The influence of these additional high risk factors on T3 levels before surgery has never been studied in our patients' population. This preoperative condition may make them prone to have a more significant low cardiac output syndrome related to ESS postoperatively.

The objective of this study was to elaborate the role of malnutrition in cardiac patients and other factors such as age, cyanosis, pulmonary hypertension and heart failure related to unrestrictive pulmonary blood flow on thyroid function as assessed by T3, T4 and TSH levels before pediatric congenital heart surgery.

Study design and procedure

Design: This is a secondary analysis of a prospective cross sectional study to evaluate the impact of malnutrition on TT3, FT3, TT4, FT4 and TSH levels before pediatric congenital heart surgery in children less than 2 years of age. We also evaluated the difference of baseline hormone levels on age at surgery, sex, type of cardiac defects (cyanotic/acyanotic) and the occurence of pulmonary hypertension or unrestrictive pulmonary blood flow before surgery. We hypothesized that malnutrition is the major factor that predicts the level of T3 before surgery.

From April 2010 until September 2010 we enrolled all patients from our pediatric cardiology and pediatric cardiac surgical service who underwent cardiac surgery and were treated in our 13-bed Pediatric Cardiac Intensive Care Unit (PCICU) at the National Cardiovascular Center Harapan Kita, Jakarta, Indonesia. In order to evaluate the baseline thyroid hormone levels, blood was collected at induction before surgery from an arterial line catheter.

Patient characteristics: Subjects included were all children between 0 and 2 years of age undergoing congenital heart surgery on cardiopulmonary bypass with an Aristotle score of 6 and above. (5) Exclusion criteria were a birth weight lower than 2 kg if the patients were neonates, preoperative tachyarrhytmia on antiarrhythmic treatment, clinical sepsis confirmed by culture, and known thyroid or metabolic disorder.

The Research Ethics Board at the National Cardiovascular Center approved this study (protocol number LB 05.01/1.4/235/2010) and written, informed consent was obtained from the parents or legal guardians.

Measured parameters: The primary outcome was the measurement of baseline serum TT3, FT3, TT4, FT4 and TSH levels. The laboratory technique used to analyze hormone levels are standard 3rd generation TSH, FT4, FT3 and TT3 assay by Abbott Microparticle Enzyme Immunoassay (MEIA) (Abbott Laboratories, Abbott Park, IL, USA). The TT4 assay used Abbott Fluorescence Polarization Immunoassay (FPIA) (Abbott Laboratories).

Data collection: Baseline clinical data were collected such as age, gender, actual weight, birth weight, nutritional status based on weight for height, (6) body length, type of heart defect (cyanotic/acyanotic), history of pulmonary hypertension and unrestrictive pulmonary blood flow before surgery.

Statistical analysis and sample size: Unpaired t test for parametric or Man Whitney test for non-parametric test were used to evaluate the difference between the group of patients with normal nutritional status and those severely malnourished in terms of their thyroid hormone levels. These tests were also used to evaluate the impact of other factors such as age, sex, type of heart disease and presence of unrestrictive pumonary blood flow on thyroid hormone levels. All calculations were done by the statistical computerized program SPSS 19 IBM serial number 5086848. Statistical significance was defined by p-values less than 0.05.

Results

Patient characteristics

A total number of 43 patients was included in this study.

The patient characteristics of the study are shown in **Table 1**. Mean patients' age was 10.17±5.80 (±SD) months with a range of 0.5-24 months; the majority of patients were older than 6 months (76.7%). The type of congenital heart defects included were isolated ventricular septal defects (VSD) in 18 cases, tetralogy of Fallot (TOF) in 15 cases, transposition of the great arteries with intact ventricular septum/or VSD (TGA IVS/VSD) in 3 cases, complete atrioventricular septal defects (CAVSD) in 2 cases and one of each case of total anomalous pulmonary vein drainage (TAPVD), pulmonary atresia with VSD (PA/VSD), double outlet right ventricle (DORV), and intermediate type AVSD. Additionally we classified the congenital heart defects into cyanotic and acyanotic and the type of pulmonary blood flow whether there was flow restriction or not. The patients showed equal numbers in terms of cyanotic (55.8%) and unrestrictive pulmonary blood flow (58.1%).

Thyroid hormone levels (TT3, FT3, T4, FT4 and TSH)

In **Table 2** the baseline thyroid hormone levels of the study population are presented. Most of the patients had normal thyroid hormone results, and only 14 (32.5%) patients showed abnormal results. Most of this subgroup had low thyroid hornone levels, including TSH. None of the patients had a high TSH. Abnormal low TT3 (<0.8 ng/ml) or FT3 (2.5 pg/ml) was shown in each of 6 (14%) individuals, low FT4 (<0.9 ng/dl) in 8 (18.6%) and low TSH (<0.4 µU/ml) in 2 patients and only 1 patients had low TT4. One patient, 6-month-old, TGA VSD, with severe malnutrition had all low FT3, TT3, FT4, and TSH results, that indicated this patient had severe euthyroid sick syndrome (ESS 2) before surgery.

Nutritional status

As many of the patients in our country may have deficiencies regarding energy input and overall nutrition, the nutritional status was determined by body weight compared to ideal body weight for specific height. (6) Subsequently, a classification was made that a patient was normally nourished when his body weight was within a 10% range of the predicted value according to his height. Mild malnourishment was defined as a weight within 10 to 15% under the predicted value, moderate was defined between 15 and 25% and severe malnourishment was found when the patient's weight was below 25% of the predicted value. As indicated in **Table 1**, the majority of our patients were moderately to severely malnourished (60.4%). In the group of 14 patients with low thyroid hormone levels, 13 patients were clinically apparent with malnutrition.

Figure 1 shows the correlation of the nutritional status to the levels of TT3 and FT3. FT3 levels in the well-nourished group were significantly higher compared to the group with severe malnourishment with FT3 levels of 4.9±0.7 vs. 3.5±0.3 pg/ml (mean±SEM, p=0.04), although most of the levels were still within normal limits (**Figure 1**). No significant difference of mean TT3 levels had been shown between severely malnourished and well nourished patients. The age distribution of patients in these two groups was equal, and mean age of the well-nourished group was higher than in the severe malnourished, but not statistically significant (8.5±4.9 vs. 10.6±5.4 months).

Age, sex, type of congenital heart diseases

There were no significant differences in thyroid hormone levels when adjusted to age groups, sex and type of congenital heart diseases as well as to the preoperative pulmonary blood flow (**Table 3**).

Discussion

In this prospective study we investigated the influence of various variables such as the nutritional status, age, sex and the type of cardiac defect on preoperative thyroid hormone levels. Thyroid hormone levels were low in a substantial group of patients before surgery (32.5%). This abnormal thyroid hormone levels in this study group can be defined as sick euthytoid syndrome (SES). One mechanism of the low T3 levels in ESS is the decline of iodothyronine deiodinase enzyme type D2 activity that converts T4 to T3, and the activation of iodothyronine deiodinase enzyme type D3 activity that increases the conversion of T4 to rT3 (reverse T3) which is biologically inactive. (7) Additionally, in severe conditions of various diseases, there is also inhibition in the central hypothalamus-pituitary axis, so that TSH also decreases together with low T3 and T4 levels. (8) This entity is described as low T3 syndrome type 2 (sick euthyroid syndrome [SES] 2 and correlated with bad outcome. (1,3,9)

In one patient of this study, not only TT3 and FT3, but also TT4, FT4 and TSH showed the typical decrease of serum levels before surgery. This typical case of SES 2 was noted in a neonate with TGA VSD and severe malnutrition. This finding is in agreement with other studies that found SES in neonates and infants is more severe than in adults. (3) None of the case studies showed increased levels of TSH that made them excluded for diagnose of congenital hypothyroidism and more as euthyroid sick syndrome.

The prevention of the typical postoperative decline of T3 level has been achieved in some studies and showed promising results, but this practice has not been accepted yet as routine management in post op pediatric cardiac surgery. (10,11) Previous studies have identified the risk groups of neonates and small children with long cardiopulmonary bypass times that showed more severe euthyroid sick syndrome. These risk groups might benefit more advantageous with postoperative T3 suplementation. (3,11) Some other risk factors such as malnutrition, a prolonged time of heart failure and hypoxemia have never been elaborated as significant risk factors for the ESS. In this study we could not demonstrate any significant impact of age and type of congenital heart defects on thyroid hormone levels, namely T3 levels. Especially cyanosis and heart failure associated with unrestrictive pulmonary blood were not determined as important factor for thyroid hormone levels in our study. Other studies however showed that almost 18-34% of heart failure cases showed lower T3 levels and this condition was significantly associated with worse outcome. (12,13)

In our study the FT3 levels in severe malnourished patients were significantly lower than those in the well-nourished group. Most previous studies also indicated similar results. (14,15) The role of leptin has been suggested in a previous review as the main controller of body weight stabilization. In a starvation state where lipid levels are low, the production of leptin decreases, and subsequently the stimulation of leptin on the TRH receptor in the paraventricular nucleus of hypothalamus also decreases, resulting in low levels of thyroid hormones. (4,16) We may assume that this mechanism can be present in our patients too, because severely malnourished patients had lower FT3 levels than well-nourished.

Most of these severely malnourished children, although clearly presenting with low FT3 levels, did not show any apparent symptoms of hypothyroidism and the TSH levels did not increase. These abnormal thyroid levels in malnutrition can be explained as an adaptive change to the illness. (14,17) Suplementation of l-thyroxine to restore serum thyroid concentrations to normal range is not indicated in this group of patients in daily practice. Some issues however have to be raised in post cardiac surgery cases. Triidothyronine suplementation is considered in some selected cases, namely in patients of high risk groups. (18) To date, no study had been done to elaborate the importance of T3 suplementation in severe malnourished patients after pediatric cardiac surgery.

Conclusion

In conclusion, patients with severe malnutrition presented with lower FT3 levels than there with normal nutrition. Severe malnutrition could be one additional risk factor for preoperative SES in cardiac patients. SES is known to be related postoperative low cardiac output syndrome after pediatric cardiac surgery. Prevention of decreased T3 levels by T3 suplementation is probably warranted in this specific group of patients to overcome the impact of SES on postoperative morbidity. Further studies are needed to elaborate the role of malnutrition on the severity of SES in pediatric cardiac surgery.

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Table 1. Baseline characteristics according to demographic data, nutritional status, type of heart defect, pulmonary hypertension and unrestrictive pulmonary blood flow before surgery.
Data presented in mean±SD, and percentage for proportion.

	All (n=43)
Age (month) <6 mo (n;%) ≥6 mo (n;%)	10.17±5,80 10 (23.3) 33 (76.7)
Male (n;%)	20 (46.50)
Birth weight (kg)	2.93±0.55
Actual weight (kg)	6.35±1.87
Height (cm)	67.47±7.69

Nutrition status (n;%)
  Overweight
  Normal
  Mild malnutrition
  Moderate malnutrition
  Severe malnutrition
	
	1 (2.3)
	10 (23.3)
	6 (14)
	13 (30.2)
	13 (30.2)

Type of heart defects (n;%)
  Acyanotic
  Cyanotic
	
	19 (44.2)
	24 (55.8)

Unrestrictive pulmonary blood flow (n;%)	25 (58.1)

Table 2. Baseline thyroid hormone levels in the study population

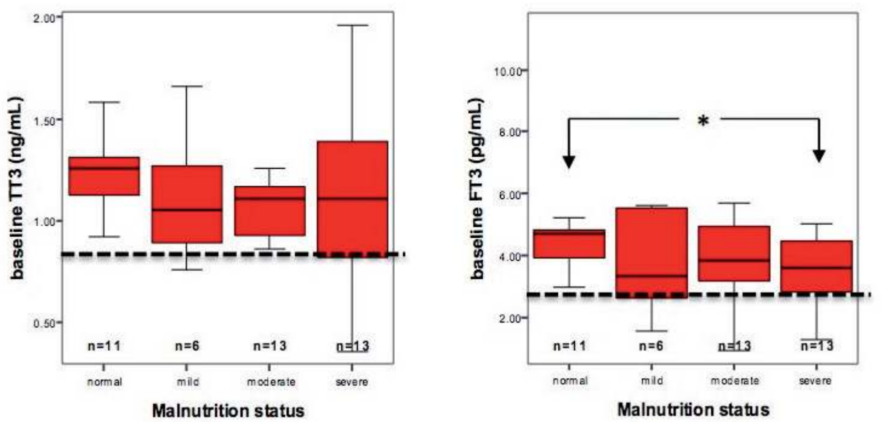
Variables (Mean±SEM)	All (n=43)
TSH (µU/ml) Min-max (NR 0.4-11)	2.88±0.29 0.28-8.95
TT4 (µg/dl) Min-max (NR 4.3-18.7)	7.67±0.23 3.82-11.38
FT4 (ng/dl) Min-max (NR 0.9-3)	1.22±0.04 0.77-1.78
TT3 (ng/ml) Min-max (NR 0.8-4)	1.13±0.05 0.36-1.96
FT3 (pg/ml) Min-max (NR 2.5-10)	3.98±0.25 0.95-11.42

Legend: TSH=thyroid stimulating hormone; TT4=total serum thyroxin; FT4=free thyroxin; TT3=total serum triidothyronine; FT3=free triidothyronine in pg/ml; NR=normal range (see text for reference). (19)

Table 3. The effect of age, sex, nutritional status, type of congenital heart disease and pulmonary blood flow before surgery on baseline thyroid hormone levels. Unpaired t test used for parametric test and Mann Whitney test for non-parametric test

Variables	TT3 (ng/ml)	p	FT3 (pg/ml)	p	TT4 (µg/dl)	p	FT4 (µg/dl)	p	TSH (µU/ml)	p
Age										
<6 mo	0.96±0.10	0.06	3.46±0.38	0.33	7.02±0.53	0.13	1.14±0.08	0.31	2.56±0.50	0.66
≥6 mo	1.18±0.06		4.14±0.31		7.87±0.26		1.24±0.05		2.97±0.34	
Sex										
Male	1.20±0.08	0.27	4.18±0.43	0.83	7.89±0.39	0.40	1.24±0.06	0.68	3.30±0.49	0.21
Female	1.08±0.07		3.80±0.31		7.89±0.29		1.20±0.06		2.46±0.31	
Nutritional status										
Normal	1.22±0.08	0.39	4.96±0.68	0.04	8.29±0.36	0.09	1.30±0.08	0.39	2.38±0.31	0.87
Severe malnutrition	1.08±0.12		3.54±0.31		7.19±0.49		1.20±0.08		2.38±0.41	
Defect										
Cyanotic	1.07±0.07	0.15	3.93±0.43	0.49	7.95±0.36	0.29	1.20±0.06	0.60	2.89±0.34	0.82
Acyanotic	1.22±0.08		4.04±0.23		7.96±0.27		1.24±0.06		2.93±0.50	
Pulmonary blood flow										
Unrestrictive	1.14±0.08	0.89	3.75±0.23	0.49	7.66±0.28	0.93	1.21±0.05	0.77	2.90±0.40	0.96
Restrictive	1.12±0.06		4.30±0.52		7.70±0.42		1.23±0.07		2.85±0.42	

Figure 1. TT3 and FT3 baseline levels based on malnutrition status



Legend: *=p<0.05 between normal and severe malnutrition in FT3, using Mann Whitney test.
Dotted line indicates lowest normal limit for each measurement.

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