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Growth assessment in down syndrome after cardiac surgery

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Abstract

Objective: To assess the effect of cardiac surgery on growth catch-up of Down syndrome (DS) children with failure to thrive (FTT) and congenital heart disease (CHD) and investigate other causes of FTT in DS children.

Method: We conducted a retrospective observational study in tertiary cardiac center from 2015 to 2018. We included all cases of DS diagnosed with CHD and FTT who completed a 1-year follow-up after cardiac surgery. We divided the cases into two groups; "normalize group" includes children who normalized their growth parameters and "underweight group" includes those who remained in FTT category during the follow-up period. We compared both groups for multiple risk factors.

Result: Most of DS had FTT upon surgery. Fifty percent of cases completed 1-year follow-up including 29 (60%) in the normalized group and 19 (40%) in underweight group. Within 6 months post-surgery, the normalized group though did not reach yet normalization of growth parameters, demonstrated statically significant improvement in weight for age, weight *Z*-score in compared to underweight group.

Within 12 months post-surgery, the normalized group achieved normalization of growth parameters and continue to show more statistically significant differences in growth parameters.

Both groups had comparable post-operation course. Univariate analysis of possible peri-operative risk factors showed no difference between both groups except for presence of untreated subclinical hypothyroidism in 58% of the underweight group versus 17% in control group ($p = 0.005$).

Conclusion: FTT in DS patient is multifactorial which needs thorough investigation and work up by multidisciplinary team. Cardiac surgery may not guarantee the improvement of growth parameters.

Keywords: Down syndrome, Post-cardiac surgery, Failure to thrive, Growth velocity

Background

Growth is the most important indicators of child health [1, 2]. FTT is an abnormal pattern of weight gain defined by the lack of sufficient usable nutrition and documented by inadequate weight gain over time with weight for age that falls below the fifth percentile [1]. CHD is one of common causes of failure to thrive in infants [2]. The influence of FTT on surgical outcome, ability of growth recovery post-surgery, and time for growth catch up post-cardiac surgery are variable [3].

Multiple studies that investigated growth catch-up post-cardiac surgery concluded that early cardiac surgery in infancy markedly improves and speeds up normalization of growth [4]. However, some patients behave differently as in cases of genetic anomalies [5].

Down syndrome is a unique population who has multiple factors that affect their growth such as heart failure, gastrointestinal pathologies, hematological and endocrine abnormalities. American Academy of Pediatrics

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in their Clinical Report in 2011 regarding health supervision for children with DS encourages initial evaluation for feeding problems between birth and 1 month of age including screening for gastrointestinal conditions such as gastroesophageal reflux, duodenal anomalies, Hirschsprung's disease and hypothyroidism [6].

Although few papers studied the progress of growth in DS patients post-cardiac surgery, the velocity of growth in patients with DS remained uncertain with the possibility of multiple contributing factors affecting growth parameters [7, 8]. The effects of corrective or palliative cardiac surgeries on short- and long-term outcome of FTT in DS are not adequately defined.

In this observational study, we focused on DS children who manifested FTT in association with CHD. We assessed their anthropometric growth parameters at the time of surgery considered as baseline, then 6 months and 1 year post-surgery. We aimed to determine prevalence of FTT in DS children requiring heart surgery, percentage of subjects who normalized their anthropometric growth parameters post-repair, average duration of time for growth catch-up to normal limit, and factors that may contribute to persistent underweight condition in this group of affected children.

Method

We conduct retrospective observational cohort study between 2015 and 2018 in Cardiac Surgical Intensive Care Unit, Prince Sultan Cardiac Centre-Qassim. All cases of DS with CHD and FTT with different age group ranging from 4 to 36 months who underwent corrective or palliative cardiac surgery and completed 12 months follow-up were included in study. Because the term 'failure to thrive' (FTT) is widely used but still no consensus exists concerning the specific anthropometrical criteria to define it [9] we selected Z score of weight to age less than − 2 Z score as a criterion to define FTT.

Growth parameters included weight, height/length were measured routinely in each outpatient visit pre- and post-surgery. The growth parameters (weight and height/length) were collected from our electronic data system and plotted on special DS growth charts upon data collection [10]. *Z*-score of weight for age, height/length for age, and weight to height/length *Z*-score were calculated using PediTools electronic calculator application [11].

We divided cases who fulfilled inclusion criteria into two groups: group 1—"normalized group" including children who normalized their growth parameters within 1-year follow-up post-surgery and group 2—"underweight group" reflected those who remained below normal growth parameters after a 1-year follow-up post-surgery. We compared both groups for multiple risk factors that may affect their anthropometric growth development pre- or during surgery such as evidence of any pre-surgical comorbidities including gastrointestinal abnormalities, hypothyroidism, feeding difficulties, gastroesophageal reflux disease, and anemia. RACHS (risk adjustment congenital heart surgery) [12], hospital length of stay (LOS), mechanical ventilation (MV) duration, vasoactive inotropes score (VIS) which was calculated by the equation {Dopamine dose (μg/kg/min) + dobutamine dose (μg/kg/ min) + 100 × epinephrine dose (μg/kg/min) + 10 × milrinone dose (μg/kg/min) + 10,000 × vasopressin dose (U/kg/min) + 100 × norepinephrine dose (μg/kg/min)}, nasogastric tube (NGT) duration, and post-operative infection.

Multidisciplinary team approach was used frequently in managing and preparing the patient pre- and post-surgery. Different subspecialties were engaged including pediatric gastroenterologist, pediatric endocrinologist, and nutritionist to optimize medical care and caloric intake in addition to optimize anti-failure medication pre- and post-surgery. Pre-surgery level of TSH above 10 mU/L was a cut-off point for diagnosis of hypothyroidism and commencing L-thyroxin.

Adherence to management plan, follow-up, and compliance to treatment were ensured and carried out using social service support.

Post-surgery, we started feeding in our cases on the second day post-surgery and the feeding were gradually increased until reaching 160–180 kcal/kg of body weight daily. In small percentage of patients when enteral feeding could not be established within a week of surgery, we supplied the patient with total parenteral nutrition until adequate enteral feeding was achieved. Feeding recommendations after discharge were given to families targeting necessary caloric intake according to child weight and age. Patients who were diagnosed as subclinical hypothyroidism discharged with medication to have follow-up with endocrinologist unfortunately we have not had a record of their thyroid status later post-surgery.

We analyzed and compared all data between both groups using GraphPad Software, San Diego, CA, USA. Continuous data were analyzed between groups using unpaired student t-test. We presented data as mean ± standard deviation of mean and $p < 0.05$ was considered statistically significant. Multivariate regression analysis was used to identify potential risk factors that may contribute to persistent FTT in operated DS children.

Result

During study period, 98 cases of Down syndrome underwent corrective or palliative surgery. Eleven patients (11%) had normal growth parameters, while all

other 87 cases had a variable degree of FTT (89%). Two cases, one with FTT and one with normal growth had in-hospital mortality, as such 96 cases of DS were discharged home from hospital (Fig. 1). Only 48 from 96 cases fulfilled the inclusion criteria of completing their follow-up at 6 and 12 months interval. We excluded others from study (Fig. 1).

Twenty-nine from 48 (60%) cases who had an average of 5–36 months improved their growth gradually and progress to normal growth parameter for age at 1 year and labeled as normalized "control group". Nineteen from 48(40%) patients aged between 4 and 18 months, failed to normalize their growth parameters and remained in FTT condition and labeled as "underweight group" (Table 1, Figs. 2 and 3).

Upon surgery both groups had *Z* score of weight to age below − 2, although it is not statistically different but underweight group demonstrated more deviation from the mean with *Z* score of weight to age − 3.75 ± 0.3 while the control group had *Z* score of weight to age − 2.86 ± 0.34.

Within 6 months post-surgery, control group though did not reach normalization of growth parameters, demonstrated statically significant improvement in weight for age, weight *Z*-score and weight to height *Z*-score in compare to underweight group (Table 1, Figs. 2 and 3).

Within 12 months post-surgery, "normalized group" achieved normalization of growth parameters and continue to show more statistically significant differences in the means of weight for age [10.69 ± 0.52 kg], weight *Z*-score [1.11 ± 0.4] and weight to height *Z* score [0.1 ± 0.26] compared to means of weight for age [8.17 ± 0.25] kg, weight *Z*-score [− 2.86 ± 0.39] and weight to height *Z* score [− 3.16 + 0.21] in "underweight group" with *P* values of 0.0001, 0.0001, and 0.0001, respectively (Figs. 2 and 3).

The pattern of growth failure in "underweight group" was in both parameters of "weight for age" and "weight for height" correlating with wasting pattern.

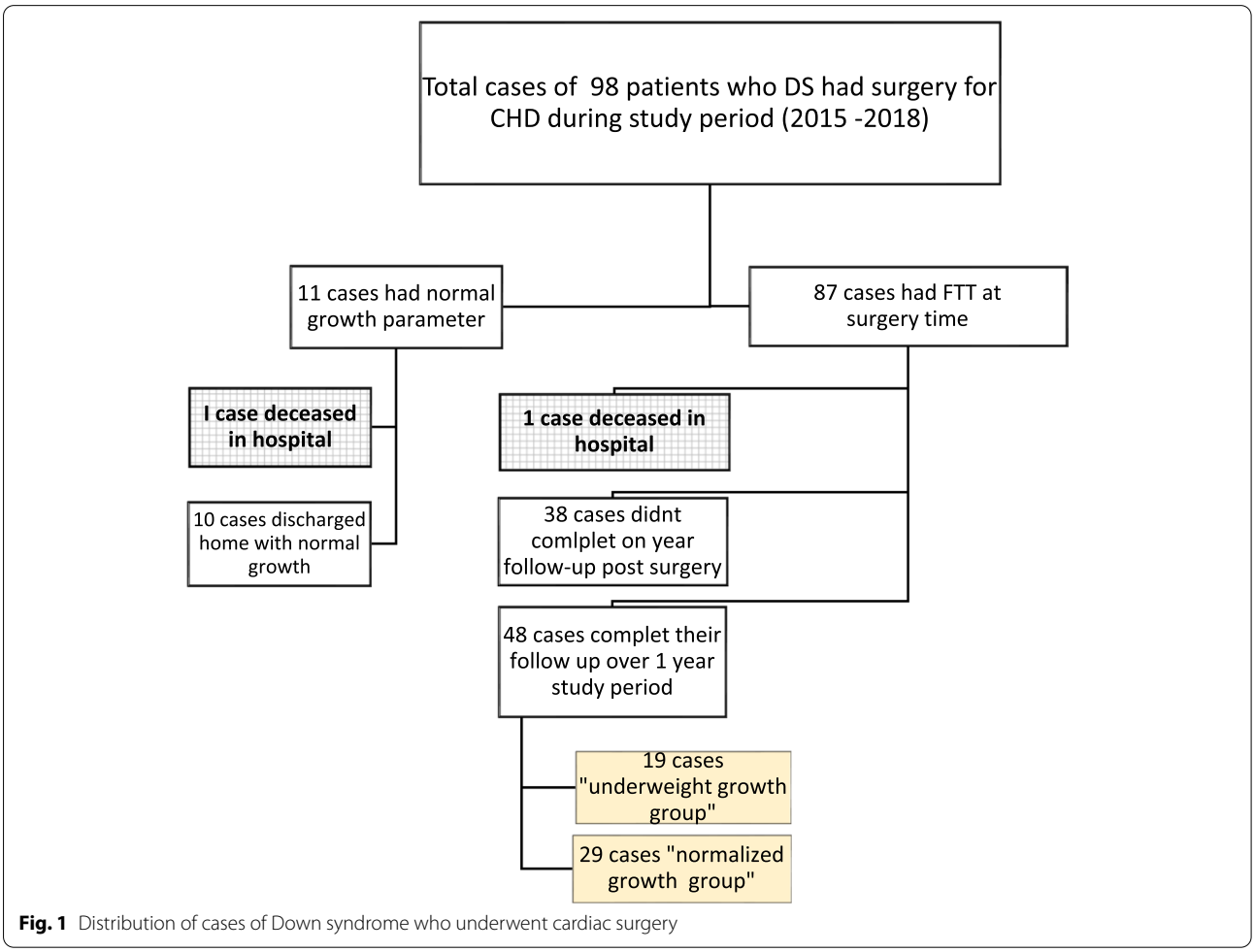

Fig. 1 Distribution of cases of Down syndrome who underwent cardiac surgery

Table 1 Growth parameter comparison between control and underweight groups and their peri-operative variables

Variable	Normalized Group $n = 29$	Underweight Group $n = 19$	*P* value
Age (month)	10±1.76 (5-36)	8.18±0.75 (4-18)	0.45
RACHS	2.8±0.09	2.57±0.11	0.11
Anthropometric Parameters at surgery			
WT at Surgery (kilogram)	6.62±0.56	5.2±0.32	0.06
Weight Z score at Surgery	-2.86±0.34	-3.75±0.3	0.05
Height at Surgery	67.9±1.97	63.57±1.01	0.09
Height Z score at Surgery	1.62±0.45	-1.75±0.23	0.8
Weight/Height Z score at Surgery	-2.6±0.5	-3.73±0.49	0.12
Anthropometric Parameters at 6 months surgery			
Weight at 6 months of follow up	8.26±0.41	6.98±0.25	**0.02**
Weight Z score at 6 months of follow up	-2.15±0.3	-3.74±0.23	**0.004**
Height at 6 months of follow up	76.6±1.88	71.15±1.08	**0.024**
Height Z score at 6 months of follow up	0.64±0.45	-1.46±0.28	**0.0006**
Weight/Height z score at 6 months of follow up	-1.72±0.3	-3.12±0.45	**0.01**
Anthropometric Parameters at 12 months surgery			
Weight at 1 year of follow up	10.69±0.52	8.17±0.25	**0.0001**
Weight Z score at 1 year of follow up	1.11±0.4	-2.86±0.39	**0.0001**
Height at 1 year of follow up	79.9±1.9	78.11±1.3	0.45
Height Z score at 1 year of follow up	0.5±0.42	-1.27±0.32	0.89
Weight/Height z score at 1 year of follow up	0.1±0.26	-3.16±0.21	**0.0001**
Predictors Variable			
Bypass time (min)	106±6.4	99±12.6	$r = -0.1, P = 58$
Cross clump time (min)	86.2±5.4	72±3	$r = -0.25, P = 0.06$
Mechanical ventilation duration (hour)	35.17±5.3	33.63±7.06	$R = -0.04, P = 0.86$
LOS (day)	8.24±0.64	8.26±1.26	$R = -0.0, P = 0.98$
Inotropes score	7.78±0.6	7.61±1	$R = -0.07, P = 0.87$
Duration of NGT feed (day)	5.45±0.9	6±2.46	$R = 0.07, P = 0.8$
Duration of antibiotic (day)	5.82±0.48	6.27±0.97	$R = 0.05, P = 0.52$

Bold indicate statistically significant *p* less than 0.05

Patients underwent either corrective or palliative surgery (Table 3), both groups did not show statistically significant differences in the studied variable, such as underline gastroenterology problem or feeding difficulties (Table 2). Thyroid function before surgery was impaired in 5 cases (17%) in control group in compare to 11 cases (58%) in underweight growth group with $P=0.006$ (Table 2). Both groups have no significant differences in residual lesion (mild mitral regurgitation) post-surgery or incidence of major complication such as arrhythmia (junctional ectopic tachycardia) or complete heart block (Table 2). We have found no correlation between RACHs, hospital long stay, or mechanical ventilation duration and failure to thrive in both groups. In addition, no correlation between some post-surgical complication such as inotropic score, nasogastric tube feeding, antibiotic use, and degree of failure to thrive (Table 1).

Discussion

Growth is fundamental to pediatric care and often used as a gauge to measure the infant's health and well-being. Growth failure is one of the more common sequelae observed in infants with CHD. Multiple factors contribute to FTT in CHD patients such as feeding dysfunction, inadequate nutrient intake because of heart failure, hemodynamic alterations in body composition related to the underlying cardiac physiology [2]. In children with Trisomy 21 hypotonia, impaired oral motor function, hypothyroidism, and gastrointestinal abnormalities may further contribute to FTT [7].

Because weight gain post-cardiac surgery may be a measure of surgical success and disease management [2], investigating other contributing factors can improve surgical and overall outcome of children with CHD.

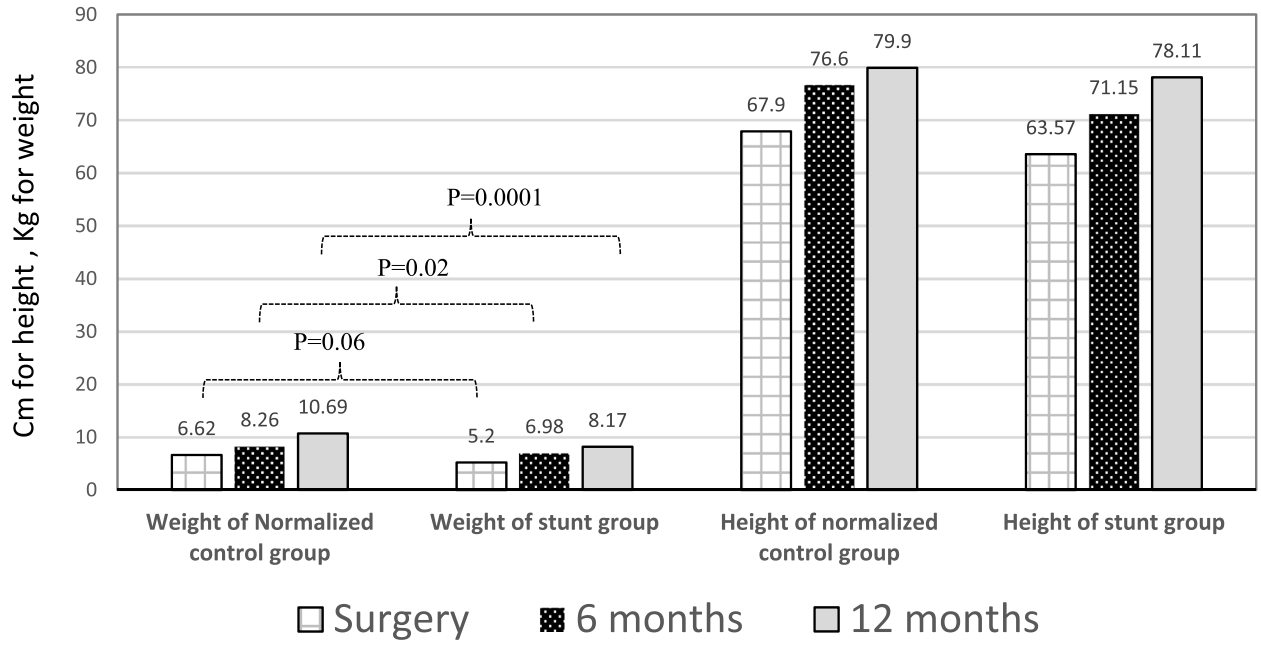

Fig. 2 Weight and height for normalized control group and underweight group at surgery, 6 months, and 1 month follow-up

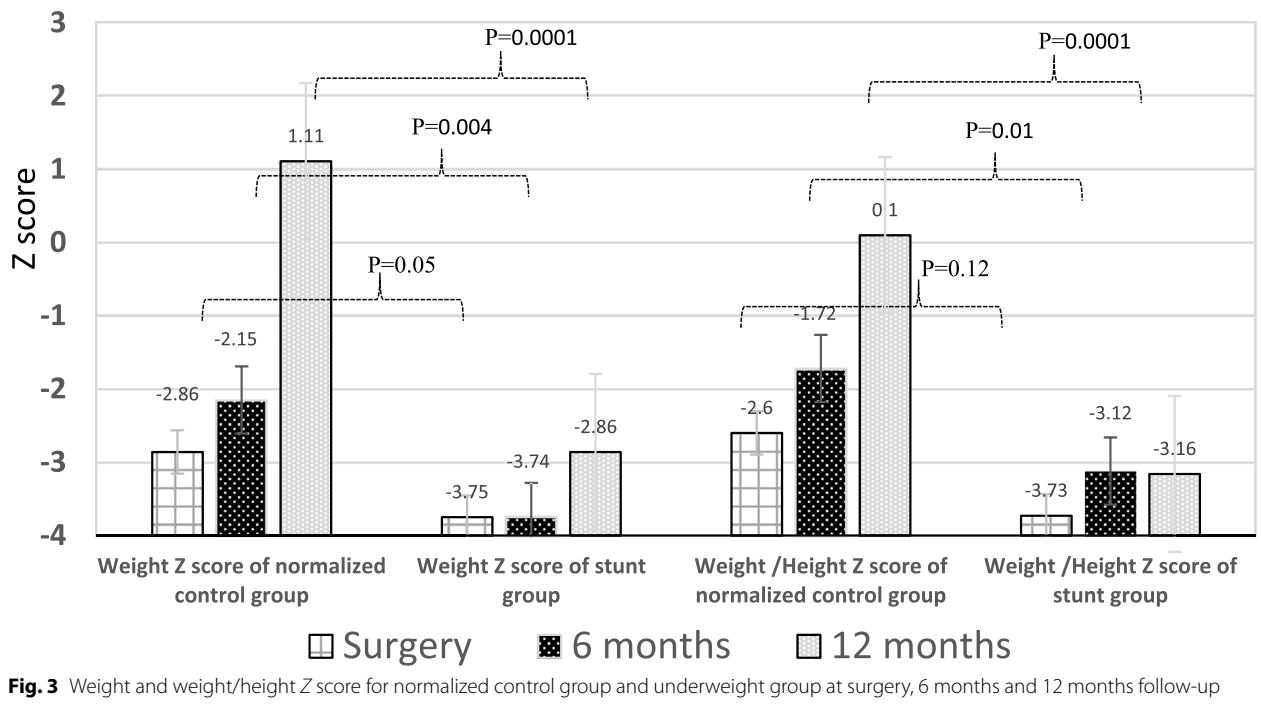

Fig. 3 Weight and weight/height *Z* score for normalized control group and underweight group at surgery, 6 months and 12 months follow-up

Although many papers that studied the effect of cardiac surgery on the progress of growth showed significant improvement of growth post-surgery compared with non-repaired group [4, 9], their findings may apply on majority of non-syndromic patients with FTT related to CHD or even preemies with CHD but not necessarily in DS population with FTT and CHD [4, 13]. In our study, we found only 60% of Down syndrome cases have achieved their normal growth after 1-year follow-up, while 40% remained in FTT category after 1 year.

Table 2 Comparison of post-cardiac surgery variables between control and underweight group

Post-operative variables	Control group *n* = 29 (%)	Underweight group *n* = 19 (%)	*P* value
Extubation failure	2 (7%)	1 (5%)	1
Noninvasive ventilation	8 (28%)	8 (42%)	0.3
Arrhythmia (Junctional ectopic tachycardia)	6 (21%)	2 (11%)	0.45
Complete heart block	1 (3.44%)	0 (0%)	0.4
Residual lesion	7 (24%)	3 (15%)	0.7
Chylothorax	3 (10%)	1 (5.3%)	1
Need for NGT	11 (38%)	6 (32%)	0.76
Pulmonary hypertension	13 (45%)	7 (37%)	0.76
Use nitric oxide	5 (17%)	0 (0%)	0.14
Discharge on sildenafil	12 (41%)	6 (32%)	0.55
Cardiopulmonary resuscitation	1 (3.5%)	0 (0%)	1
Subclinical hypothyroidism	5 (17%)	11 (58%)	**0.005**
Palliative surgery (pulmonary artery banding)	5 (17%)	4 (21%)	1
Gastro oesophageal reflux	2 (7%)	2 (11%)	1
Gastrointestinal abnormality	0	1	
Feeding difficulty	2	2	

Bold indicate statistically significant *p* less than 0.05

Nathalie [8] and her group studied the growth recovery in DS patient and concluded that all her cases achieved their desired growth parameters after 1-year follow-up. Mackman et al. [7] demonstrated catch-up growth of DS patients post-atrioventricular septal defect but normalized growth achieved only after 2 years of age. Genetic comorbidity is claimed in other study as the most significant factor for poor weight gain post-cardiac surgery [5].

More than one third of our patients failed to recover their growth following cardiac surgery with 33% of all our cases and 58% in underweight group had subclinical hypothyroidism which was accidentally discovered during routine investigations pre surgery and most probably overlooked during neonatal screening and could contribute to their FTT.

Subclinical hypothyroidism (SH) (transient hypothyroidism) is frequently encountered in DS. SH refers to isolated elevation of TSH with normal thyroid hormone levels [14].

Its prevalence varies between 7 and 40% [14, 15]. Because it may manifest only with mild thyrotropin (TSH) elevation with normal T4, it may be overlooked as normal during neonatal screening.

Several studies have shown that commencing L-thyroxin to neonates with DS in the first 2 years of life can improve their growth and neurological development [15, 16].

American Academy of Pediatrics (AAP) guideline recommends treating DS neonate with subclinical hypothyroidism if TSH remains higher than 10 mU/L during first month follow-up [17].

There are other risk factors of FTT that need to be evaluated as potential causes of delayed growth after cardiac repair. Vaidyanathan et al. [18] found that malnutrition persisted in 27.3% of patients post-cardiac surgery and was associated with a birth weight of $\leq$ 2.5 kg, poor nutritional status at presentation, and height of parents. In our study, both groups did not show significant differences in the evidence of GIT disorder or the feeding difficulties or uncontrolled heart failure before surgery, and all of them received nutritional support pre- and post-surgery.

The correlation between the severity of congenital heart disease and the FTT is not proven to affect growth parameters. Manso et al. [19] studied the growth pattern of VSD patients who underwent cardiac surgery and he failed to find relations between the size of VSD and severity of FTT, however he showed that earlier repair is a better predictor of improving FTT. In our study, both groups of patients had similar RACHS score with comparable surgical complexity and comparable age at the time of repair (Tables 1 and 2). Hence, it is unlikely that age, or type of surgery whether palliative or corrective are contributing factors to persistent FTT condition in underweight group (Table 3).

Table 3 Underline congenital heart disease in both groups of patients

	GROUP (1)	GROUP (2)
AVSD repair	18	7
VSD repair	5	7
Pulmonary artery banding	5	4
Others	1 (Coarctation of aorta)	1 (Tetralogy of Fallot)

Because of their lower protein and energy reserves, FTT patients may be particularly vulnerable to the hyper catabolic state that frequently happens following heart surgery, at higher risk for nosocomial infections, prolonged wound healing, and prolonged hospitalization. Some papers linked FTT and post-surgical comorbidities [20] even increase mortality [21]. However, there is little evidence to support the notion that lower weights are associated with poorer surgical outcomes [22].

We found that both groups had non-significant differences in post-operation complication such as duration of mechanical ventilation or LOS or infection (Table 2). Similar findings were presented in a recent prospective study of 1028 infants and advocated early correction of CHDs irrespective of nutritional status [23]. Preoperative optimization of nutritional status through aggressive feeding is unnecessary according to study in most patients, although it may make sense to use this technique if there are ongoing delays in access to surgical repair [22].

Although FTT in Down syndrome carries significant challenges in intensive care unit, implantation of good nutritional support pre- and post-surgical repair targeting high calorie intake will help to decrease the risk factors of failure to thrive in intensive care unit. Nevertheless, the small number of cases and retrospective nature of our study make it impossible to generalize results. Larger group of patients and longer follow-up duration may be needed to enhance powerful outcome.

Conclusion

FTT is common in infant with DS and CHD. Although it is not an obstacle of surgical repair but the surgical repair alone, may not improve and normalize growth parameters. Early and an extensive investigations for other causes of FTT is mandatory to enhance better outcome in these population.

Abbreviations

FTT: Failure to thrive; DS: Down syndrome; CHD: Congenital heart disease; ICU: Intensive care unit; LOS: Length of hospital stay; MV: Mechanical ventilation; NGT: Nasogastric tube; TSH: Thyroid stimulating hormone; SH: Subclinical hypothyroidism; VSD: Ventricular septal defect; RACHS: Risk adjustment Congenital heart surgery.

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Authors' contributions

I, the undersigned, corresponding author of this manuscript, agree to the conditions stated above and certify that my co-authors and I have contributed to all of the following: Mesned Abdulrahman: constructing the idea and hypothesis of research planning the methodology to reach the conclusion in addition to supervising and organizing the course of project. Abdullah AL Qwaee: planning the methodology to reach the outcome, provide material by referring patients. Ali Alakhfash: planning the methodology to reach the conclusion in addition to supervising and organizing the course of project read and adjust final manuscript and approved it. Tageldein Mohamad: constructing the idea of project, provide necessary literature review, and critical review of the manuscript. Mohamed S. Kabbani: constructing the hypothesis of stud, share in data analyses process, critical review to manuscript several times, and approved the final manuscript. Usama Alseedi: share in data organizing and cleaning, present data analyzing, and refer patient to participate in project. Baraa Obedien: share in data collection. Abdulaziz Chrit: data collection and cleaning, search references and present data analysis, share some parts of manuscript writing. Lastly, all authors read and agreed final manuscript.

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Availability of data and materials

Material and data collection was send during submission. The datasets analyzed during the current study by GraphPad Software San Diego, CA, USA, is available in https://www.graphpad.com/quickcalcs.

Declarations

Ethics approval and consent to participate

Al Qassim Institutional board committee (reference number not available) agreed the proposal of study and the participate consent on 03/02/2015, individual consent to share the study and publish it was signed by parents before data collection.

Consent for publication

After full counselling, parents signed agreement of publishing the collected data.

Competing interests

The authors declare that they have no competing interests.

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