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Assessment of Vitamin D Level and Nutritional Status in Children with Cholestatic Disorders

Sarah Abdelrashid*[1], Nehal El Koofy[1], Mona Fathy[2], Engy A. Mogahed[1], Rokaya Mohamed Elsayed[1]
Department of Pediatrics[1], Department of Clinical and Chemical Pathology
[2] Kasr Alainy Medical School, Cairo University, Cairo, Egypt
Corresponding Author: Sarah Abdelrashid, **E-mail:** sararashid.558@gmail.com,
Orcid number: 0000000219290031, **mobile phone:** 01060590333

ABSTRACT

Background: Malnutrition and vitamin D deficiency is a frequent complication in children with chronic cholestatic disorders. **Objective:** This study aimed to assess nutritional status and serum level of vitamin D in children with chronic cholestasis. **Methods:** Forty infants and children (1–6 years) with cholestatic liver diseases were enrolled from the Pediatric Hepatology Department, Cairo University Children's Hospital. Nutritional history, anthropometric measurements [including weight, height, mid-upper arm circumference (MUAC) and triceps skin fold (TSF)] and serum vitamin D were assessed. Vitamin D was correlated with liver functions. Assessment of nutritional status was performed using subjective nutritional global assessment (SGA) and nutritional risk screening tool STRONGkids.

Results: The mean age of the patients was 2.7 ± 1.67 and 67.5% were males. The most frequent diagnosis was biliary atresia (42.5%) followed by cholestasis with normal GGT (32.5%) then cholestasis with high GGT (25%). Although, all patients were on regular doses of oral vitamin D, the number of vitamin D deficient patients was 13 (32.5%). Vitamin D is not correlated with liver functions. Anthropometric measurements showed that TSF was the most accurate parameter to detect malnutrition (77.5% of patients were below fifth percentile). About 47 and 72 % of the patients had malnutrition according to SGA and STRONGKids respectively.

Conclusion: Malnutrition and vitamin D deficiency are common among cholestatic children despite regular oral supplementations. MUAC and TSF are effective applied anthropometric measures for nutritional assessment. Vitamin D is not correlated to the liver functions.

Keywords: Anthropometry, Children, Cholestasis, Nutritional assessment, Vitamin D.

INTRODUCTION

The nutritional status is significantly impacted by cholestatic liver disorders (CLD) throughout infancy (when growth rates are at their peak), thus lowering the quality of life for cholestatic children with advanced liver dysfunction [(1)].

The results of a pediatric liver transplant are strongly impacted by it. Therefore, it is essential to offer appropriate nutritional care in order to stop worsening liver injury and raise the likelihood that a liver transplant would be feasible [(2)].

Every child with chronic cholestasis requires a basic nutritive screening, followed by an adjustment and follow-up strategy at intervals optimal for the patient's clinical condition and documented in their care records [(3)].

In children with CLD, vitamin D deficiency can range from 10% to 36%. Deficiencies in the hepatic conversion of vitamin D2 or D3 to the hydroxylated molecule, inadequate dietary intake, reduced supply of bile salts necessary for absorption of fat-soluble vitamins, or reduced production of the protein that binds vitamin D may all contribute to this [(4)].

Owing to the down regulation of bile acid transport and metabolism, loss of the anti-inflammatory and immunomodulatory effects, and amplification of the adverse effects of cholestasis with bile duct ruptures, vitamin D deficiency induces progressive liver disorders [(5)].

This study's purpose was to measure serum vitamin D level as well as nutritional status among children suffering from cholestatic liver disorders.

METHODS

This was a cross-sectional analysis that was conducted at the Pediatric Hepatology Unit, Cairo University Specialized Children's Hospital. Our research engaged 40 infants and children with a diagnosis of chronic cholestatic disorder of both sexes with age from 1-6 years with the duration of illness > 6 months.

Exclusion criteria: Patients with end stage liver disease and cases associated with other chronic diseases that may affect the anthropometric measures and nutritional status were excluded.

The following steps were carried out on each patient:

1. Medical history emphasizing symptoms of liver disease (age, sex, diagnosis, jaundice, dark urine, acholic stool, steatorrhea, itching, bleeding tendency and encephalopathy). Developmental history (motor and mental milestones) and drug history [all included patients were receiving oral vitamin D (2000 IU daily in infants and 3000 IU in older children) among other fat-soluble vitamins). Nutritional history included the following:
   - Frequency and duration of GI symptoms: vomiting, diarrhea, steatorrhea, and distension.
   - Twenty-four hours recall and food frequency

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(carbohydrates, proteins, vegetables, fruits, legumes, dairy products).

2. General examination laying stress on:

- Anthropometric assessment including height, weight, body mass index (BMI) that were plotted on Standard Egyptian growth curves [6]. Triceps skin fold thickness was measured by skin fold caliper (Harpenden calipers). It allows estimation of fat energy stores and is useful for serial monitoring. Mid-upper arm circumference (MUAC) was measured by obtaining the mid-upper arm, which is the point halfway between the acromion of the shoulder and the olecranon of the elbow (marked with a pen) then we take the readings made with a non-stretch tape measure at the mid-upper arm point, which was plotted on growth curves (values below fifth percentile were considered abnormal) [7].
- Physical signs of nutrients deficiency:

Assessment of nutritional status using subjective nutritional global assessment (SGA) and nutritional risk screening tool STRONGkids (Screening Tool for Risk on Nutritional status and Growth) [8].

Laboratory investigations

Complete blood picture, liver functions (serum total and direct bilirubin, alanine aminotransaminase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP], and gammaglutamyl transferase [GGT], prothrombin time [PT], prothrombin concentration [PC] and international normalized ratio [INR] and serum albumin). Serum vitamin D was measured by chemiluminescence method on Elecsys Autoanalyzer (vitamin D deficiency was defined as vitamin D (25-OH) of <20 ng/ml and insufficiency as 21-29 ng/ml).

Ethical approval:

This research was conducted in conformity with the Declaration of Helsinki, which is the World Medical Association's code of ethics for studies involving humans and being approved by The Ethical Committee Institutional Review Board of Kasr Alainy Medical School, Cairo University prior to patients' enrollment. All patients became enrolled in the study after an expressed approval that was gained from parents.

Statistical methods

Data were statistically characterized as mean with standard deviation (SD), median (interquartile range [IQR]), or frequencies (number of instances) and percentages. Quantitative data were compared using Mann Whitney test for the nonparametric data. P value ≤ 0.05 was considered statistically significant. Correlation was done using Spearman's correlation statistics. All statistical calculations were done using computer program SPSS (statistical package for the social science; SPSS Inc., Chicago, IL, USA) release 15 for Microsoft Windows (2006).

RESULTS

Our investigation included 40 children with chronic cholestasis; 27 (67.5%) were males. Mean age of the patients was 2.7 ± 1.67 ranging between 1-6 years. The most frequent diagnosis was biliary atresia (42.5%) (All had a successful Kasai operation) followed by cholestasis with normal GGT (32.5%) including progressive familial intrahepatic cholestasis (PFIC) type 1 and 2 and bile acid synthetic defect then Alagille syndrome (12.5%) and undiagnosed cases of cholestasis (12.5%).

Regarding developmental history, 22 patients (55%) had delayed sitting ranging between 7-12 months, 24 (60%) had delayed crawling ranging between 10-24 months, walking was delayed in 10 patients (25%) ranging between 18-30 months, and delayed ascending stairs in 10 (25%) ranging between 24-36 months.

Cereals were the most frequent food received by the studied patients at time of enrollment to the study (95%) **(Table 1)**.

Table (1): Type of food received in the study group (n=40)

	Frequency	Percentage
Cereals	38	95
Legumes	23	57.5
Dairy products	23	57.5
Fruits	21	52.5
Vegetables	21	52.5
Fast food	20	50
Soft drink	13	32.5
Proteins	6	15

Anthropometric measures showed that 37.5% of the patients were underweight, 32.5% had short stature, 37.5% had low MUAC and 77.5% had low TSF (below fifth percentile) **(table 2).**

Table (2): Anthropometric measures among studied patients (n=40)

	Weight No of patients (%)	Height No of patients (%)	MUAC No of patients (%)	TSF No of patients (%)
<3rd	11 (27.5)	10 (25)	0 (0)	0 (0)
3rd	2 (5)	1 (2.5)	0 (0)	0 (0)
3rd-5th	2 (5)	2 (5)	15 (37.5)	31 (77.5)

MUAC: mid-upper arm circumference, **TSF:** triceps skin fold

Signs of vitamin or nutrient deficiency were present in 16 patients (40%) **(Table 3).**

Table (3): Signs of vitamins and nutrients deficiency among studied patients (n=40)

	Number of patients with positive findings	Percentage
Lack of nail luster	6	15
Dental caries	5	12.5
Apathy	5	12.5
Dermatitis	3	7.5
Brittle nails	3	3
Xerosis	2	5
Follicular keratosis	1	2.5
Ecchymosis	1	2.5
Edema	1	2.5
Peripheral neuropathy	0	0
Hypoactive reflexes	0	0
Hair color changes	0	0
Spoon shaped nails	0	0
Angular stomatitis	0	0
Glossitis	0	0
Metaphyseal widening	0	0
Genu varum	0	0
Genu valgum	0	0
Swollen painful joints	0	0

Nutritional assessment showed that 21 patients (52.5%) were normally nourished according to SGA while 19 patients (47.5%) were moderately malnourished. On the other hand, nutritional assessment by STRONGKids showed that 29 patients (72.5%) were at medium risk of malnutrition and 11 patients (27.5%) were at high risk. Complete blood count of the study group revealed that 36 patients (90%) were anemic with hemoglobin level ranging between 4.69 and 14.2 g/dL; out of them 22 patients had microcytic hypochromic anemia (red cell distribution width (RDW) was increased in 17 patients), 14 patients had normocytic normochromic anemia.

Fifteen patients (37.5%) had thrombocytopenia (ranging between 55 and 720).

Liver functions among studied patients are shown in (**Table 4).**

Table (4): Liver functions among studied patients

Liver functions	Results	Normal range
Total bilirubin (mg/dL) Median (IQR)	4.5 (31)	<1.2 mg/dl
Direct bilirubin (mg/dL) Median (IQR)	2.4 (14.5)	<0.2 mg/dl
AST (IU/L) Median (IQR)	104.5 (375)	Up to 60 U/L
ALT (IU/L) Median (IQR)	75 (209)	Up to 45 U/L
ALP (IU/L) Median (IQR)	515 (354)	Up to 640 U/L
GGT (IU/L) Median (IQR)	167.5 (880)	<45 U/L
PT (seconds) Median (IQR)	13.6 (2.7)	<15 seconds
PC (%) Median (IQR)	90 (26)	<70%
INR Median (IQR)	1 (0.2)	<1.3
Albumin (g/dL) Median (IQR)	3.8 (1.2)	3.5-5 g/dl

ALP: alkaline phosphatase, **ALT:** alanine aminotransferase, **AST:** aspartate aminotransferase, **GGT:** gamma glutamyl transpeptidase, **INR:** international normalized ratio, **IQR**: interquartile range, **PC:** prothrombin concentration, **PT:** prothrombin time**, SD**: standard deviation.

The mean of serum vitamin D level of all patients in our study was 40.5 ± 27.2 ranging between 3-85 ng/ml. Thirteen patients (32.5%) had vitamin D deficiency with mean ±SD was 10 ±5.07 ranging between 3-16.5 and 2 (5%) had vitamin D insufficiency ranging between 24-26.2 ng/ml. Delayed dentition was more common in vitamin D deficient patients (36%) in which the percentage in patients with normal serum level of vitamin D was 13%, however, no statistically significant difference was reached.

There was an insignificant correlation between vitamin D and all anthropometric indicators; weight/age (P=0.04; r=0.32), stature/age (P=0.6; r= 0.07), MUAC (P=0.4; r= 0.1), TSF (P=0.2; r= 0.1) among studied patients.

Vitamin D did not correlate with each of total bilirubin (p=0.07; r= 0.28), direct bilirubin (p=0.2; r=-0.33), PT (p=0.09; r=-0.27) and INR (p=0.1; r=-0.22) albumin (p=0.8; r=0.02) **(Table 5).**

Table (5): Comparison between patients with and without vitamin D deficiency regarding liver function

	Patients with normal serum vitamin D level (n=25)	Patients with vitamin D deficiency or insufficiency (n=15)	P value
Total bilirubin (mg/dL) Median (IQR)	4 (19.4)	5 (30.8)	0.3
Increased Total bilirubin No of patients (%)	20 (80)	13 (86.7)	0.5
Direct bilirubin (mg/dL) Median (IQR)	1.7 (14.2)	4.4 (14.4)	0.2
Increased Direct bilirubin No of patients (%)	16 (64)	12 (80)	0.2
AST (IU/L) Median (IQR)	104 (370)	105 (283)	0.9
Elevated AST No of patients (%)	21 (84)	11 (73.3)	0.4
ALT(IU/L) Median (IQR)	75 (209)	75 (184)	0.5
Elevated ALT No of patients (%)	18 (72)	10 (66.7)	0.7
ALP(IU/L) Median (IQR)	523.5 (361)	515 (356)	0.6
Elevated ALP No of patients (%)	8 (32)	3 (20)	0.4
GGT (IU/L) Median (IQR)	175 (880)	147 (492)	0.9
Elevated GGT No of patients (%)	23 (92)	13 (86.7)	0.5
Albumin (g/dL) Median (IQR)	3.5 (1.1)	3.8 (1.6)	0.5
Low serum albumin No of patients (%)	8 (32)	5 (33.3)	0.9
PT Median (IQR)	13.6 (2.8)	14.6 (5.5)	0.2
Prolonged PT No of patients (%)	13 (52)	10 (66.7)	0.3
INR Median (IQR)	1.05 (0.57)	1.13 (3.39)	0.4
Elevated INR No of patients (%)	3 (12)	4 (26.7)	0.2

ALP: alkaline phosphatase, **ALT:** alanine aminotransferase, **AST:** aspartate aminotransferase, **GGT:** gamma glutamyl transpeptidase, **INR:** international Normalized ratio, **IQR**: interquartile range, **PC:** prothrombin concentration, **PT:** prothrombin time, **SD**: standard deviation.

DISCUSSION

In order to achieve appropriate nutrition status, regular nutrition assessment is essential since it enables the early identification of malnutrition in cholestatic children [(9)].

Children's nutritional status is evaluated to determine who needs additional nutrition support and to monitor therapy outcome in individuals with chronic liver disease. At the initial appointment and all consecutive visits, nutritional status should be evaluated [(10)].

A substantial percentage of our patients had delayed motor milestones. This can be attributed to malnutrition in addition to the mechanical effect of organomegaly and ascites. Malnutrition is a significant consequence of CLD that can increase mortality and morbidity rates in persons of all ages, but particularly in young children because of their developmental requirements. Diminished bile acid-dependent absorption of lipids and fat-soluble nutrients causes malnutrition [(11)]. Chronic enteropathy secondary to associated portal hypertension, inadequate dietary intake, higher energy demands, and endocrine dysfunction are further mechanisms [(12)]. Insulin-like growth factor (IGF-1) and its primary circulating binding protein, IGF binding protein 3, are mostly produced by the liver (IGF-BP3). Growth hormone's anabolic effects are enhanced by IGF-1 (GH). The GH/IGF-1 axis is compromised in cholestatic liver disorders due to decreased IGF-1 and IGF-BP3 synthesis. IGF-1 levels tend to decline as a result of GH resistance due to downregulation of GH receptors [(13)].

Regarding anthropometric assessment of our patients, percentage of patients who were below 5th percentile for age and sex as regards weight was 37.5%, stature was 32.5%, was MUAC 37.5% and TSF was 77.5%. **Mansi *et al.* [(14)]** detected malnutrition in a larger number of patients with chronic liver disease, when they used skinfolds and MUAC, which were 56% by MUAC and 59.4% according to TSF below 5th percentile, while 35.6% were underweight and 49% were stunted below 3rd percentile. Children with CLD may have imprecise standard weight and height measures due to fluid overload, ascites, and organomegaly [(13)]. Consequently, arm anthropometrics can be used as a substitute method to detect malnutrition because it can assess lean muscle and fat reserves [(15)]. Due to fact that edema accumulates less in the upper extremities, they are still fairly reliable even when there is fluid retention [(16)]. In the research published by **Maio *et al.* [(17)]**, the midarm circumference was the optimal anthropometric parameter to correlate the muscle mass deficiency with seriousness of hepatocellular impairment. The changes in these parameters can appear earlier than height, which make them significant tools for assessing early malnutrition [(17)]. Because persistent cholestasis impairs nutrition throughout infancy, when growth rates are at their maximum, it compromises the clinical prognosis of

cholestatic infants with liver failure [18] and is present in about 80% of cases [1].

In the present study, the mean of serum vitamin D level of all patients were ranging between 3-85 ng/ml. Thirteen patients (32.5%) had vitamin D deficiency ranging between 3-16.5 and 2 (5%) had vitamin D insufficiency ranging between 24-26.2. In a study done by **Anwar *et al.* [19]**, they reported a prevalence of 56% of vitamin D deficiency (values lower than 20 ng/ml) in cholestatic children with mean value of 37.9 ± 28.2. **Marilia and Themis [20]** observed that cholestatic children had a prevalence of vitamin D deficiency of 36% (values lower than 9 ng/ml), with a mean average value of 13.07 ±8.39 ng/ml. Regardless of using the oral supplement as recommended, hypovitaminosis D still occurred. **Shen *et al.* [21]** stated that oral formulation recipients may exhibit lower compliance.

In our study, we found no statistically significant differences in anthropometry in normal and deficient vitamin D patients apart from TSF with borderline significance. **Marilia and Themis [20]** did not find any correlation between serum vitamin D levels and nutritional condition, duration of cholestasis and consistent vitamin supplementation.

We found no correlation between vitamin D and total bilirubin (P=0.5), direct bilirubin (P=0.2), AST (P=0.4), ALT (P=0.7), alkaline phosphatase (P=0.4) and GGT (P=0.5). This is contrary to what was reported in **Shen *et al.* [21]** study that found total bilirubin (P<0.02) and direct bilirubin (P<0.03), had a statistically significant association with vitamin D deficiency.

The strength of our work is that vitamin D deficiency among cholestatic children has been reported despite regular oral supplementation, and therefore monitoring of vitamin D concentrations is essential or high doses may be needed especially in severe cases.

Limitations: Our major study limitation was the small sample size. Moreover, the cross-sectional nature of the study was another limitation, as we did not perform a follow up for the vitamin D deficient patients after dose adjustments.

CONCLUSION

In conclusion, malnutrition and vitamin D deficiency are common among cholestatic children despite regular oral supplementations. MUAC and TSF are effective applied anthropometric measures for nutritional assessment.

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