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Sarcopenia in Children with Chronic Liver Diseases: What Behind the Scene?

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Abstract

Background: Sarcopenia should be considered as one of the main component of malnutrition in chronic liver diseases (CLD).

Aim of Study: To assess the utility of ultrasound in detection of sarcopenia in children with chronic liver disease.

Patients and Methods: The present study was conducted as a case control study included 77 children with CLD, who attended Pediatric Hepatology, Gastroenterology and Nutrition Department at our institution, and 62 age and sex matched healthy children as controls. Each child underwent: Full history taking, thorough clinical examination, laboratory investigations and assessment of sarcopenia. The primary outcome of the study was the utility of (ultrasound) US in detection of sarcopenia in children with CLD. Statistical analysis was performed using mixed methods.

Results: There wasa statistically significant difference between diseased and healthy groups regarding echogenicity of biceps brachii, layer thickness, cross sectional area and echogenicity of rectus femoris (*p*-value=0.000, 0.018, 0.003 & 0.000). There was a statistically significant difference between diseased and healthy groups regarding total body fat range, total body fat mass, right limb fat range, right limb fat mass, left limb fat range and left limb fat mass (*p*-value= 0.048, 0.02, 0.013, 0.02, 0.007 & 0.024, respectively).

Conclusion: There was a significant association between CLD in children and decreased muscle mass and strength especially in lower limb. US was able to detect early sarcopenic changes in diseased children while bioelectrical impedance analysis (BIA) which is a commonly used tool couldn't detect any muscle changes between healthy and diseased groups.

Key Words: *Pediatric – Hepatic disease – Electric impedance – Quadriceps muscle – Muscle mass and function.*

Introduction

THE association between chronic liver diseases (CLD) and malnutrition, both in adults and pediatric patients, has been known for a long time. The impaired nutritional status was demonstrated which can increase complications and reduce life expectancy in CLD patients [1]. In addition to monitoring liver function parameters, the evaluation of the nutritional status, mainly by body composition, represents an extremely important measure. This evaluation allows the measurement of adiposity and skeletal muscle mass [2].

In the last decades, it has been suggested that muscle wasting should be considered the main component of malnutrition in CLD. The reduction in muscle mass is nowadays better defined as sarcopenia which was initially described as a physiologic process during aging, but chronic diseases may considerably anticipate this event (secondary sarcopenia) [3].

The definition of sarcopenia includes both a decrease in muscle mass and reduced muscle function; the importance of focusing on muscle function to confirm sarcopenia and the need to provide clear cut-off points (for age, sex and ethnicity) to identify patients with muscle impairment have been recently recommended by the revised European consensus on the definition and diagnosis of Sarcopenia [4]. The assessment of muscle function is crucial for the assessment of sarcopenia since muscle strength is not linearly related to muscle mass. However, this measurement is also frequently missing in studies assessing sarcopenia in children [5]. The aim of this study was to assess the utility of ultrasound in detection of sarcopenia in children with chronic liver diseases.

Patients and Methods

The present study was conducted as a case control study in Pediatric Hepatology, Gastroenterology and Nutrition Department of National

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Liver Institute, Menoufia University from October 2018 to April 2020. Informed written consents were obtained from parents of all children before their involvement in the study to ensure their approval to participate in research and to publish. All study procedures were carried out and approved by the Ethical Committee of Menoufia Faculty of Medicine in September 2019. Participant's names were kept on a password-protected database and linked only with a study identification number for this research. The present study was conducted as a case control study included 77 children with chronic liver diseases and 62 ages and sex matched healthy children as controls.

Inclusion criteria were: Age was above 6 (youngest age for hand grip strength testing) and below 18 years old.

Exclusion criteria were: Patients with known muscle diseases, high serum creatine phosphokinase, and patients with known neurological disorders that were associated with muscle atrophy, patients with malignancy, patients with chronic diseases other than their chronic liver condition, comatose patients and patients on corticosteroid therapy.

Each child underwent: Full history taking, thorough clinical examination, laboratory investigations and assessment of sarcopenia which included; anthropometric measures, functional muscle assessment and skeletal muscle ultrasonography. Assessment of pediatric end stage liver disease (PELD) score for chronic liver disease patients < 12 years old PELD score uses the patient's values for serum bilirubin, serum albumin, the international normalized ratio (INR), whether the patient has growth failure (<-2 standard deviation) and whether the patient is less than 1 year old, to predict survival. It is calculated according to the following formula PELD = 4.80[serum total bilirubin (mg/dL)] + 18.57[INR] - 6.87 [albumin (g/dL)] + 4.36 (zero to 10 were considered moderate liver disease. Results >10 were considered sever liver disease **[6]**.

Assessments of model for end-stage liver disease (MELD) scorefor chronic liver disease patients >12 years old. MELD uses the patient's values for serum bilirubin, serum creatinine, and the international normalized ratio for prothrombin time (INR) to predict survival. It is calculated according to the following formula. MELD = 3.78x [serum total bilirubin (mg/dL)] + 11.2x [INR] + 9.57x [serum creatinine (mg/dL)] + 6.43 MELD Na = MELD - Serum Na - [0.025 * MELD * (140 - Serum Na)] + 140. Results from zero to 10 were considered mild liver disease. Results from >10 to 20 were considered moderate liver disease. Results >20 were considered sever liver disease **[7]**.

Assessment of Child-Turcotte-Pugh score Child-Turcotte-Pugh score is a universal scoring system of the degree of liver failure in patients with cirrhosis. Variables measured by this system include ascites, encephalopathy, serum albumin, bilirubin, and (International Normalized Ratio) INR. Each variable is scored 1-3, with 3 indicating most severe derangement. Total points are used to assign a grade in the Child-Pugh scoring system [child A (total score: 5-6); child B (total score: 7-9) and child C (total score: 10 -11)]. The higher total score in PELD, MELD or Child score means more severe liver disease with bad prognosis **[8]**.

Assessment of right rectus femoris and biceps brachii muscles by the following parameters: 1. Muscle mass: (A) Muscle layer thickness. (B) Cross sectional area 2. Muscle echogenicity: Fat infiltration in muscle (myosteatosis) increases its echogenicity (become brighter than normal). Muscle mass and echogenicity of right rectus femoris and biceps brachii muscles were measured by diagnostic ultrasound device (Philips, X matrix, iu22) with a linear array transducer L12-5 MHz (Mega Hertz). All measurements were made by a single trained and certified sonographer. Ample amounts of water-soluble transmission gel were applied to the transducer in order to maintain adequate acoustic contact with the skin surface. Imaging was completed while the participants were relaxed in recumbent position with extension of knee and elbow. Minimal examiner pressure was exerted during the scanning to attain sufficient image resolution. Captured images were saved and echogenicity was determined using a computer assisted grey-scale analysis offered by ImageJ software program **[9]**.

Gray scale analysis in the cross-sectional ultrasound image, the target area was cropped as an elliptical selection to perform gray scale analysis. The result images were analyzed on Intel® Core I3® based computer using ImageJ software with a specific built-in routine for pixel statistics. The software routine includes pixel intensity measurement and analysis, to construct a 3dimentional histogram, from which mean pixel intensity was calculated for each image. Values were ranged from 0 (absolute black) to 255 (absolute white) (Fig. 1). All results were exported as excel sheet **[10]**.

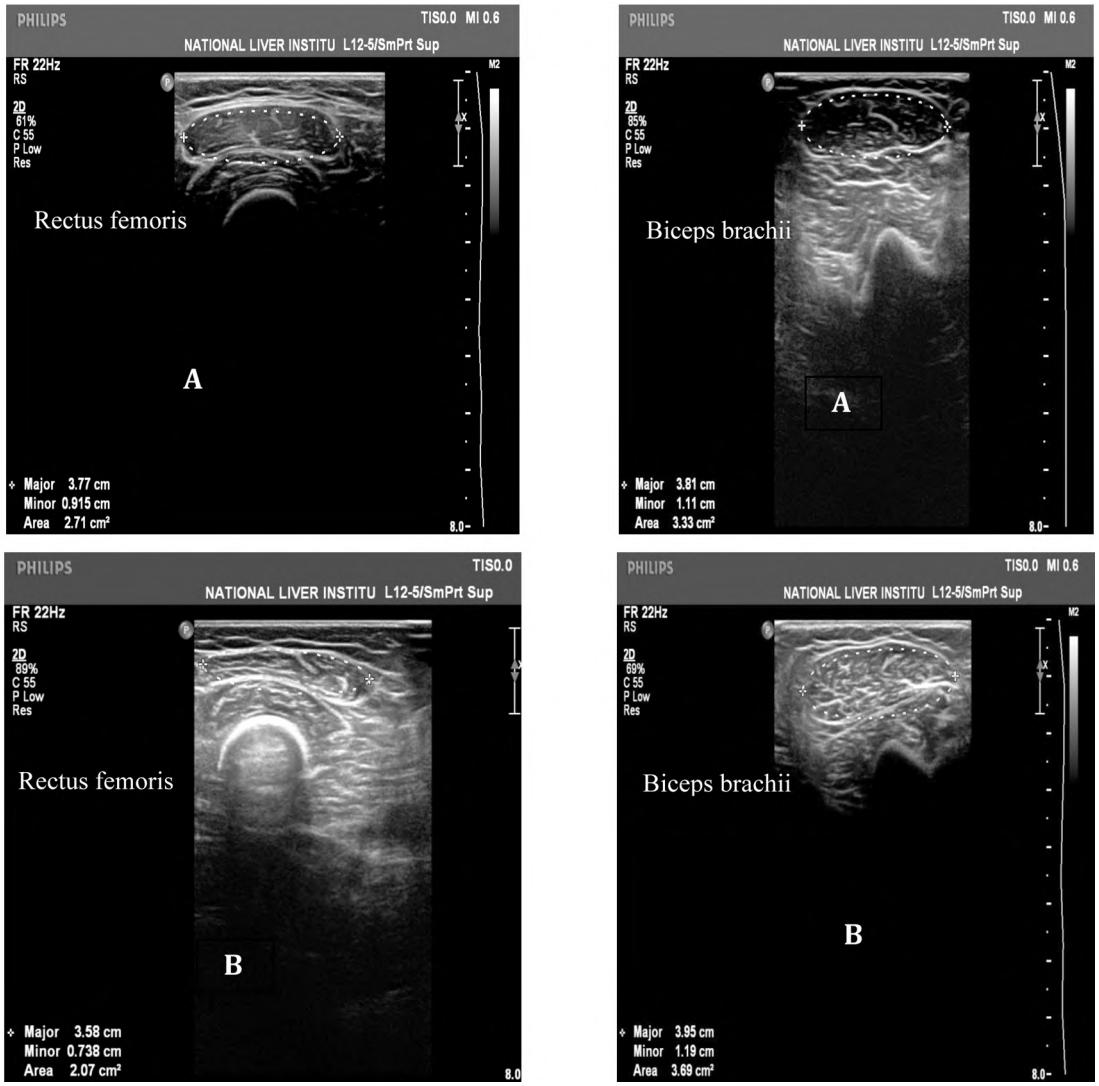

Fig. (1): Pictures of Ultrasonic cross-sectional area (ellipse mark) showing different echogenicity between healthy (A) and diseased muscles (B).

Statistical analysis:

Data were collected and entered to the computer using SPSS (Statistical Package for Social Science) program for statistical analysis (version 21) (IBM Corp., Released 2012). The results were considered significant when the probability of error is less than 5% (p-value $\leq$ 0.05).

Results

There was a statistically significant difference between diseased and healthy groups regarding echogenicity of biceps brachii, layer thickness, cross sectional area and echogenicity of rectus femoris (p-value=0.000, 0.018, 0.003 & 0.000). However, there was no statistically significant difference between both groups regarding layer thickness and cross-sectional area of biceps brachii (p-values=0.052 & 0.142, respectively) (Table 1).

There was a statistically significant difference between diseased and healthy groups regarding total body fat range, total body fat mass, right limb fat range, right limb fat mass, left limb fat range and left limb fat mass (p-value=0.048, 0.02, 0.013, 0.02, 0.007 & 0.024, respectively). However, there was no statistically significant difference between both groups regarding total body fat free mass, total body muscle mass, phase angle, right arm fat range, right arm fat mass, right arm fat free mass, right arm muscle mass, right limb fat free mass, right limb muscle mass, left arm fat range, left arm fat mass, left arm fat free mass left arm muscle mass, left limb fat free mass and left limb muscle mass (p-value=0.411, 0.409, 0.154, 0.582, 0.101& 0.428, 0.387, 0.74, 0.744, 0.245, 0.109, 0.511, 0.543, 0.833, 0.815, respectively) (Table 2).

Table (1): Comparison between the patient group and control group as regards muscle ultrasound.

Parameters	Diseased (n=77) Mean ± SD	Healthy (n=62) Mean ± SD	Independent Samples Test	p-value
Biceps brachii layer thickness (cm)	1.02±0.29	1.13±0.36	1.964	0.052
Biceps brachii cross sectional area (cm)	3.26±1.52	3.67±1.7	1.477	0.142
Biceps brachii echogenicity	103.26±21.68	84.22±17.96	5.661	<0.001*
Rectus femoris layer thickness (cm)	0.98±0.27	1.09±0.28	2.396	0.018*
Rectus femoris cross sectional area (cm)	2.70±1.22	3.57±1.96	3.070	0.003*
Rectus femoris echogenicity	130.45±24.35	105.58±25.67	5.844	<0.001*

N: Number of patients. SD: Standard deviation. *: Statistically significant (p<0.05).

Table (2): Comparison between the patient group and control group as regard bioelectrical impedance analysis.

Parameters	Diseased (n=77) Mean ± SD	Healthy (n=62) Mean ± SD	Independent Samples Test	p-value
Whole body parameters:				
Fat Range (%)	22.61±7.06	24.87±6.07	1.997	0.048*
Fat Mass (kg)	1.85±1.31	2.40±1.43	2.351	0.020*
Fat Free Mass (kg)	30.82±13.30	32.49±10.59	0.824	0.411
Muscle Mass (kg)	29.20±12.67	30.80±10.12	0.828	0.409
Angle Phase	5.08±0.84	5.26±0.55	1.434	0.154
Right arm parameters:				
Fat Range (%)	33.54±7.78	34.18±5.78	0.551	0.582
Fat Mass (kg)	0.59±0.38	0.70±0.33	1.651	0.101
Fat Free Mass (kg)	1.25±0.78	1.35±0.64	0.794	0.428
Muscle Mass (kg)	1.19±0.73	1.29±0.6	0.868	0.387
Right limb parameters:				
Fat Range (%)	26.45±8.7	29.85±7.12	2.53	0.013
Fat Mass (kg)	1.85±1.31	2.40±1.43	2.315	0.02
Fat free Mass (kg)	5.21±2.71	5.35±1.97	0.333	0.74
Muscle Mass (kg)	4.97±2.55	5.10±1.86	0.327	0.744
Left arm parameters:				
Fat Range (%)	34.09±8.26	35.61±6.82	1.167	0.245
Fat mass (kg)	0.66±0.46	0.78±0.42	1.1615	0.109
Fat free Mass (kg)	1.31±0.77	1.38±0.61	0.659	0.511
Muscle Mass (kg)	1.24±0.71	1.31±0.58	0.610	0.543
Left limb parameters:				
Fat Range (%)	26.61±8.4	30.19±6.98	2.745	0.007
Fat Mass (kg)	1.83±1.3	2.35±1.41	2.276	0.024
Fat Free Mass (kg)	5.09±2.63	5.17±1.9	0.212	0.833
Muscle Mass (kg)	4.86±2.47	4.94±1.78	0.226	0.815

N: Number of patients. SD: Standard deviation. *: Statistically significant (p<0.05).

The rectus femoris echogenicity (%) was a statistically insignificant discriminator for PELD score severity (moderate or severe) with Area under the ROC curve (AUC)=0.522 (95% CI 0.358-0.682) (Z=0.179, p=0.8581) (Fig. 2). The rectus femoris echogenicity (%) was a statistically significant discriminator of MELD score severity category (Moderate or Severe) death with Area under the ROC curve (AUC)=0.688 (95% CI 0.515-0.830) (Z=2.103, p=0.0355). The diagnostic criterion using Youden index was the level of >125.7 with a sensitivity of 100% (95% CI 54.1-100.0), specificity of 51.61% (95% CI 33.1-69.8) Positive predictive value (PPV) of 28.6% and negative predictive value of 100.0% (Fig. 3). The rectus femoris echogenicity (%) was a statistically insignificant discriminator for Child class with Area under the ROC curve (AUC)=0.565 (95% CI 0.448-0.678) (Z=0.628, p=0.5302) (Fig. 4).

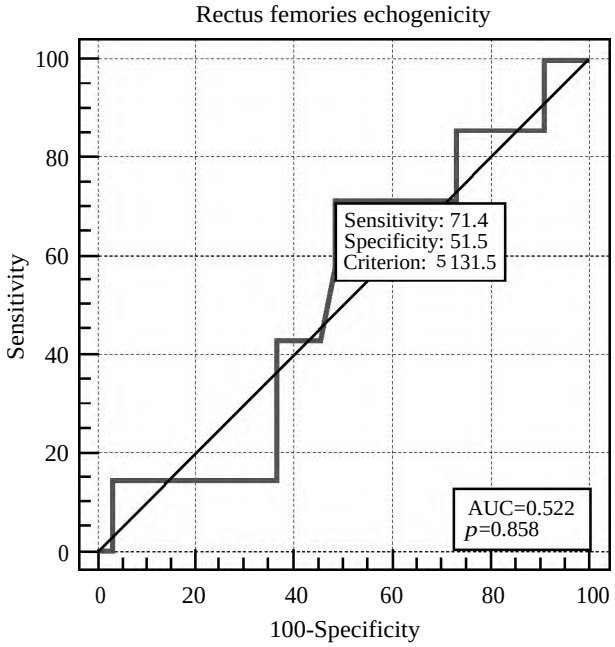

Fig. (2): Area under the ROC curve of rectus femoris echogenicity for discrimination of PELD score severity (moderate or severe).

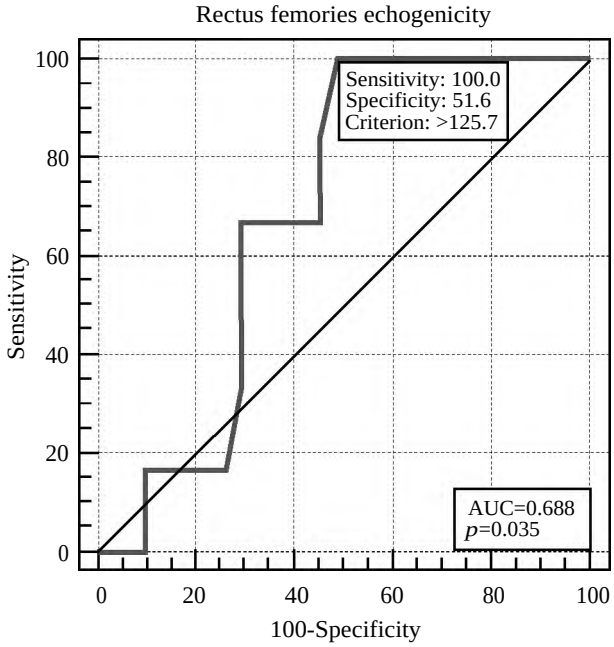

Fig. (3): Area under the ROC curve of rectus femoris echogenicity for discrimination of MELD score severity (moderate or severe).

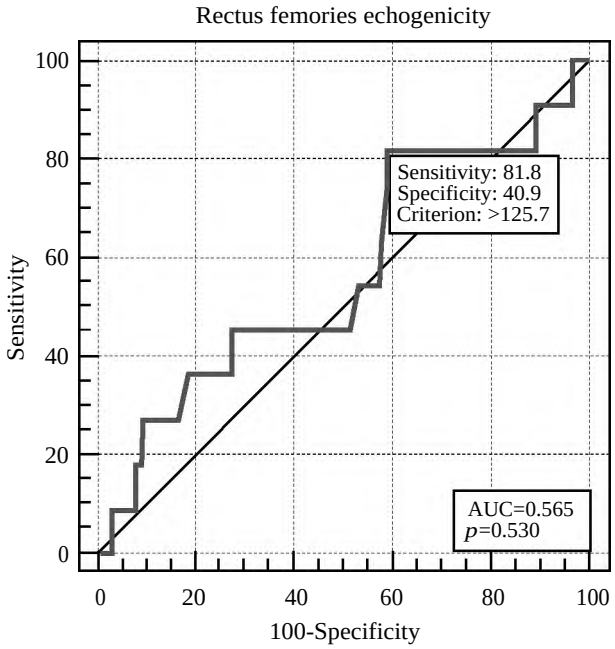

Fig. (4): Area under the ROC curve of rectus femoris echogenicity for discrimination of Child class (B or C).

Discussion

The present study showed a statistically significant decrease in layer thickness and cross-sectional area of rectus femoris muscle estimated by US in diseased group as compared with control healthy group. On the other hand, there was a statistically non-significant decrease in in layer thickness and cross-sectional area of biceps brachii muscle estimated by US in diseased group as compared with control healthy group. However, there was a statistically significant increase in US echogenicity of both muscles (rectus femoris and biceps brachii) in diseased group as compared with control healthy group. Several studies on old patients reported that decline of muscles mass with aging does not progress at the same rate throughout the whole body and anterior thigh muscles with abdominal muscles, which are predominantly contains fast twitch type 2 muscle fibers, undergo atrophy earlier than those of the upper and other lower limb muscles. Muscles composed mainly from type 1 fiber (e.g., tibialis anterior) or have equal distribution of two fiber types (e.g., anterior forearm muscles) were found to be less changed by aging. In addition, upper limb muscles may actually not undergo atrophy but instead display a compensatory hypertrophy. As such, loss of regional muscle mass may not be determined with measurements which estimates total muscle mass (e.g. DXA) **[11-13]**.

Although there are no published studies on children that support regional sarcopenia, the results of our study seem to be consistent. Regional or site-specific sarcopenia may explain why results of our study showed significant decrease in rectus femoris muscle mass without significant decrease in biceps brachii muscle mass in diseased group and also can explain why sit to stand test was significantly decreased in diseased patients without significant decrease in hand grip, mid arm circum-

ference or calf circumference. Our results are in agreement with several studies on old persons which showed a decrease in US based measures of thigh muscles mass without associated decrease of muscles mass in other anatomic sites such as upper limbs and these results were confirmed by CT. Most of these studies proposed that rectus femoris can be considered as an early biomarker of Sarcopenia **[11,14-16]**.

In our study, absence of a statistically significant decrease in muscle mass by BIA in diseased group may be explained by low sensitivity or accuracy of this technique as most of the cases were suffering from mild disease and needs highly sensitive technique to detect early muscle changes. Moreover, regional sarcopenia if it is proven true, we can consider it another explanation because BIA estimate all body or limb muscles and sarcopenia usually starts in certain muscles as quadriceps muscle. So, the non-affected muscles can mask sarcopenic significance of the affected muscles.

Conclusion:

Ultrasound which is a newly diagnostic tool of sarcopenia was able to detect early sarcopenic changes in diseased children while BIA which is a commonly used tool couldn't detect any muscle changes between healthy and diseased groups. Finally, a sarcopenic changes seem to be starting in large muscles like thigh muscles and tools which can evaluate size and strength of these muscles like US and sit to stand test respectively can enable us for early detection of sarcopenia.

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الهزال العضلى عند الأطفال المصابين بأمراض الكبد المزمنة : ماذا وراء الكواليس ؟

فى العقود الماضية، تم اقتراح أن الهزال العضلى يجب اعتباره المكون الرئيسى لسوء التغذية فى مرضى الكبد المزمن. يتم تعريف الانخفاض فى كتلة العضلات فى الوقت الحاضر بشكل أفضل على أنها الهزال العضلى والتى تم وصفها فى البداية على أنها عملية فسيولوجية أثناء الشيخوخة، ولكن الأمراض المزمنة قد تتوقع هذا الحدث بشكل كبير.

المرضى وطرق الدراسة : أجريت هذه الدراسة كدراسة حالة ضابطة وضمت ٧٧ طفلاً يعانون من أمراض الكبد المزمنة و ٦٢ طفل من الأطفال الأصحاء المتطابقين فى العمر والجنس كعناصر تحكم.

النتائج : توجد فروق ذات دلالة إحصائية بين المجموعات المريضة والصحية فيما يتعلق بتولد الصدى فى العضدية ذات الرأسين، وسمك الطبقة، ومنطقة المقطع العرضى، وتوليد الصدى للفخذ المستقيمة (القيمة الاحتمالية = ٠.٠٠٠، ٠.٠١٨، ٠.٠٠٣، ٠.٠٠٠). ومع ذلك، لا يوجد فرق معتد به إحصائياً بين المجموعتين فيما يتعلق بسمك الطبقة ومنطقة المقطع العرضى للعضلة ذات الرأسين العضدية (القيمة الاحتمالية = ٠.٠٥٢ و ٠.١٤٢ على التوالى).

الخلاصة : الفحص بالموجات فوق الصوتية وهى أداة تشخيصية حديثة لمرض الهزال العضلى قادرة على الكشف عن التغيرات المبكرة للهزال العضلى فى الأطفال المرضى. يبدو أن التغيير الناتج عن الهزال العضلى قد بدأ فى عضلات كبيرة مثل عضلات الفخذ والأدوات التى يمكنها تقييم حجم وقوة هذه العضلات مثل الفحص بالموجات فوق الصوتية والجلوس لاختبار الو قوف على التوالى يمكن أن تمكننا من الكشف المبكر عن الهزال العضلى فى الأطفال.