Serum level of insulin like growth factor-1 in children with chronic liver disease

Prepared by: Hany Fathy Ahmed

Supervised by:

Dr. Ehab Mohamed Eid, Professor of Public Health, Institute of Postgraduate Childhood Studies, Ain shams University.

Dr. Moushira Erfan Zaki, Professor of Human Genetics, Biological Anthropology Department, National Research Centre.

Dr. Rokaya Mohamed El-Sayed, Professor of Pediatrics, Faculty of Medicine, Cairo University.

Dr. Mona Anwar Mohamed, Professor of Medical Biochemistry, National Research Centre.

Abstract

Background: Malnutrition and growth retardation are important consequences of CLD in childhood. Although IGF is a marker of protein metabolism, that can be used to assess malnutrition. However, in CLD, with impaired IGF synthesis, its use may lead to an exaggeration of the degree of malnutrition. Objectives: to determine the level of IGF-1 in these patients and to demonstrate the relation between its level and the degree of malnutrition and the degree of hepatic dysfunction. Methodology: Fifty children with CLD, recruited from the outpatient clinic of pediatric hepatology and from the pediatric hepatology department of Pediatric Hospital, Cairo University, were enrolled in the study. Their mean age was 2.05 years (ranged from 0.5 to 5.75 years). They were compared with an age and sex-matched normal healthy children (control group). Anthropometric measurements, liver function tests and serum level of IGF-1 were performed. Assessment of severity of liver disease was done using the modified Child-Pugh score. Results: Results revealed that serum IGF-1 level was significantly lower in patients compared to controls, and it was significantly lower in Child Pugh C compared to Child Pugh B and A, and it was significantly lower in Child Pugh B compared to Child Pugh A. Moreover, there was no significant correlation between any of the anthropometric parameters and serum IGF-1. Conclusion: In CLD, IGF-I level is inversely correlated to the degree of liver dysfunction rather than the degree of malnutrition.

Key words: - IGF-1- Children - Chronic Liver Disease

مستوى عامل النمو شبيه الإنسولين-1 فى مصل الأطفال المصابين بأمراض الكبد المزمنة

المستخلص

مقدمة: إن تأخر النمو و سوء التغذية من أكبر المشاكل التى يعاني منها الأطفال المصابون بأمراض الكبد المزمنة. بالرغم من أن عامل النمو شبيه الإنسولين-1 هو أحد دلائل عملية أيض البروتينات و بالتالى إمكانية إستخدامه فى تقييم الحالة الغذائية إلا أن إنخفاض تكوينه عن طريق الكبد فى حالات الإصابة بأمراض الكبد المزمنة يجعل إستخدامه فى تقييم الحالة الغذائية غير دقيق حيث يؤدي إستخدامه إلى تقييم زائد لدرجة سوء التغذية . الهدف من البحث: قياس مستوى عامل النمو شبيه الإنسولين-1 عند الأطفال الأطفال المصابين بأمراض الكبد المزمنة وتحديد مدى علاقة مستواه بدرجة تدهور الحالة الوظيفية للكبد ودرجة سوء التغذية. المنهجية: تم إجراء هذه الدراسة علي50 طفل(25 ذكر-25 أنثى) مصابين بأمراض الكبد المزمنة بأسبابها المختلفة والذين يترددون علي عيادة الكبد والمحتجزين بقسم الكبد بمستشفي الأطفال جامعة القاهرة وقد تراوحت أعمارهم من 6 شهور -75, 5 سنة (متوسط العمر 01 ,2 سنة) و تمت مقارانتهم بأطفال أصحاء من نفس الفئة العمرية للمرضى ومن كلا الجنسين (المجموعة الضابطة). و تم عمل قياسات أنثروبومترية, وظائف كبد و قياس مستوى عامل النمو شبيه الإنسولين-1. كما تم قياس درجة الخلل الوظيفي للكبد باستخدام مقياس تشايلد باج المعدل .نتائج البحث: أظهرت النتائج إنخفاض مستوى عامل النمو شبيه الإنسولين-1 فى المرضى عنه فى المجموعة الضابطة. وكان مستواه يتناسب عكسيا مع درجة الخلل الوظيفى للكبد. كما لم تثبت الدراسة وجود علاقة ذات قيمة إحصائية بين مستوى عامل النمو شبيه الإنسولين-1 وأي من المعايير الأنثروبومترية. الخلاصة : مستوى عامل النمو شبيه الإنسولين- 1 يتناسب مع الحالة الوظيفية للكبد وليس الحالة الغذائية.

الكلمات المفتاحية: عامل النمو شبيه الإنسولين-1- الأطفال- أمراض الكبد المزمنة

Introduction

Chronic liver disease (CLD) is a disease process of the [liver](http://en.wikipedia.org/wiki/Liver) that involves a process of progressive destruction and regeneration of the liver [parenchyma](http://en.wikipedia.org/wiki/Parenchyma) leading to [fibrosis](http://en.wikipedia.org/wiki/Fibrosis) and [cirrhosis](http://en.wikipedia.org/wiki/Cirrhosis) (Shepherd, 2008).

Insulin-like growth factor-I (IGF-I) is a polypeptide hormone that functions as the major mediator of growth hormone (GH)-stimulated somatic growth, as well as a mediator of GH-independent anabolic responses in many cells and tissues. (Bonefeld and Møller, 2011; Clemmons, 2012; [Puche and](http://www.ncbi.nlm.nih.gov/pubmed?term=Puche%20JE%5BAuthor%5D&cauthor=true&cauthor_uid=23148873)  [Castilla-Cortázar,](http://www.ncbi.nlm.nih.gov/pubmed?term=Castilla-Cort%C3%A1zar%20I%5BAuthor%5D&cauthor=true&cauthor_uid=23148873) 2012).

Malnutrition and growth retardation are important consequences of CLD in childhood. They are associated with frequent complications, hospitalization, poor outcome after liver transplantation, and ultimately death (Roongpisuthipong, 2001; Hurtado-López et al., 2007).

The pathogenesis of malnutrition in CLD is multifactorial and includes a reduction in nutrient and caloric intake, anorexia and dietary restrictions, impaired intestinal absorption, abnormalities in nutrient metabolism, and increased proinflammatory cytokine levels, resulting in a hypermetabolic state (Sanchez and Aranda-Michel, 2006; Hurtado-López et al., 2007; Nightingale and Ng, 2009). A disturbed growth hormone (GH)–insulin-like growth factor (IGF-1) axis may also contribute to wasting and growth failure in children with liver disease, by virtue of IGF-1 deficiency and GH resistance (Shepherd, 2008).

The nutritional status has a great influence on IGF-I. Both the energy and protein content of the diet are important in the maintenance of IGF-1(Livingstone, 2013). Although IGF is a marker of protein metabolism, that can be used to assess malnutrition. However, in CLD, with impaired IGF synthesis, its use may lead to an exaggeration of the degree of malnutrition (Stephenson et al., 2001; Taylor and Dhawan, 2005; Socha, 2008). Moreover, Colakoğlu et al., 2007; Dehghani et al., 2012; [Khoshnood](http://www.ncbi.nlm.nih.gov/pubmed?term=Khoshnood%20A%5BAuthor%5D&cauthor=true&cauthor_uid=23599716)  et al., 2013 and [Ronsoni](http://www.ncbi.nlm.nih.gov/pubmed?term=Ronsoni%20MF%5BAuthor%5D&cauthor=true&cauthor_uid=23619263) et al., 2013 reported a decrease of IGF level in patients with CLD, and they found that its level was correlating to the extent of hepatic dysfunction rather than the degree of malnutrition.

The IGF-I deficiency in CLD is thought to result primarily from the reduced synthetic capacity of the hepatocellular mass, combined with a decrease in GH receptors in the cirrhotic liver (Donaghy et al., 2002).

Aim of the study

* To measure the level of IGF-1 in children with CLD and to identify the relation between its level and the degree of malnutrition and the degree of hepatic dysfunction.

Subjects and methods

* Subjects
* This is a cross- sectional case control study that included 50 children with CLD (25 males and 25 females) recruited from the outpatient clinic of pediatric hepatology and from the pediatric hepatology department of Pediatric Hospital, Cairo University in the period from April 2012 to April 2013. Their mean age was 2.05 years (ranged from 0.5 to 5.75 years). They were compared with an age and sex-matched normal healthy children (26 males and 24 females) attending the pediatric general clinics and pediatric emergency department, with a mean age of 2.01 years (ranged from 0.5 to 5.83 years).

All the subjects met the inclusion and exclusion criteria mentioned below

 Inclusion criteria:

* Children with chronic liver disease.
* Age range: 6 months to 6 years.
* Both sexes were included.

Exclusion criteria:

* Associated chronic disease such as neurological, heart, or renal diseases.
* Children with diabetes mellitus.
* Age less than 6 months or more than 6 years.

Ethical Considerations

The parents were informed about the purpose of the study and cases were included in the study only after written consent was given by parents. The study protocol was approved by the Ethical Committee of the National Research Centre and the Institute of Postgraduate Childhood Medical Studies, Ain Shams University.

* Methods

All participating children were subjected to

History taking: This include: age, sex, age at onset of the liver disease, symptoms of liver cell failure.

* Physical examination: involved
* General examination: Head, neck, limbs, skin, back, spine, and genitalia.
* Systemic examination: (Neurological, cardiovascular, chest, abdominal examination) to identify level of consciousness, signs of liver cell failure, organomegaly, ascites, and to exclude associated chronic diseases such as neurological, heart, or renal diseases.
* Anthropometric assessment:

Anthropometric assessment was performed using standardized equipments, and following the recommendations of the International Biological Program (Tanner et al., 1969). All bilateral measurements were taken on the left side. Three consecutive measurements were taken and when the differences between the readings were acceptable the mean was recorded.

Body weight (Kg): Children < 2 years old were weighed on Seca scale. While children ≥ 2 years of age were weighed while standing on a digital platform scale. Subjects were measured without shoes and minimal clothing. The measure was recorded to the nearest 0.1 kg.

Body length (cm) (for children <3 years of age): Length was measured and recorded to the nearest 0.1 cm in a recumbent position using an infantometer. The assistant held the child’s head in firm contact with the headboard, so that the Frankfurt plane is vertical. At the same time the legs are straightened, holding the feet with toes pointed up and moving the footboard against the feet.

Height (cm) (for children >3 years): Height was measured and recorded to the nearest 0.1 cm using a standiometer with a movable block. The subjects were measured while standing, without shoes, with their heels together and back as straight as possible and arms hanging freely; the head was positioned in the Frankfort horizontal plane and the movable block was brought down until it touched the subject’s head.

Mid upper arm circumference (MUAC) (cm): It was measured using a flexible, non-stretchable measuring tape with the arm completely relaxed and the measurement was taken horizontally, midway between the inferior border of the acromion process and the tip of the olecranon process. The tape was just touching the skin but not compressing the tissue. The measure was taken to the nearest 0.1 cm.

Skin-fold thickness (mm): This was measured by using Holtain skin-fold caliper. The thumb and four fingers of the left hand picked up a fold of skin and subcutaneous tissue and pinched it away from the underlying muscle. Readings were taken to the nearest 0.2 mm as soon as the caliper came in contact with the skin and the dial reading stabilized.

* Triceps skin-fold thickness (mm): The tips of the acromion process and olecranon were palpated, and a mark was made on the skin (a point midway between them and parallel to the long axis of the arm). Then the skin-fold was picked up between the index finger and the thumb of the left hand, over the posterior surface of the triceps muscle, one centimeter above the mark then the caliper jaws were applied.
* Subscapular skinfold thickness (mm): The subject's shoulders were erect and the arm beside the body. The skinfold was picked up at the inferior angle of the scapula then the caliper jaws were applied.

Total upper arm area (TUAA), mid upper arm muscle area (MUAMA), and mid upper arm fat area (MUAFA) were calculated with MUAC and TSFT measurements according to the formulas described by Jeliffe (1963); Gurney and Jelliffe (1973); Sann et al. (1988) and Frisancho (1990) and the results were expressed in square millimeters.

* MUAMA (cm2) (MUAC [cm]  [TSF ×π])2/(4 ×π)
* TUAA (MUAC)2 (cm)/(4 ×π)
* MUAFA (cm2) TUAA MUAMA
* AFI=100 × (AFA/ TUAA)
* Where π3.14

The results of anthropometric data of these patients were compared with that obtained from the measurements on normal healthy Egyptian children (Egyptian Growth Charts, 2002). All anthropometric data were expressed in standard deviation score (z score) to allow comparison of data irrespective of age and sex. The calculation was made according to the following formula:



* Laboratory investigations:
* The following investigations were done: Aspartate aminotransferase (AST), alanine aminotransferase (ALT), gama glutamyltransferase (GGT), alkaline phosphatase (ALP), serum albumin, serum bilirubin (total and direct), prothrombin time, and international normalized ratio (INR). Procedures: Venous blood samples (5mL) were withdrawn, 1mL was collected into heparinized tube for determination of prothrombin time. The rest of the sample was collected into plain tube and allowed to clot, and then serum was separated and stored at -20 °C until assayed by Hitachi automated chemical analyzer using commercially available kits according to the manufacturer’s instructions.
* Serum IGF-1 was measured using quantitative Enzyme-Linked Immuno-Sorbent Assay (ELISA) using commercial kit provided by DIAsource, Belgium according to the manufacturer’s instructions.
* Assessment of the severity of liver disease: : It was done using Modified Child-Pugh score which classifies severity of liver disease according to the degree of ascites, the plasma concentrations of bilirubin and albumin, the prothrombin time, and the degree of encephalopathy .

Table (1): Modified Child-Pugh score

|  |  |
| --- | --- |
| Points Assigned | Parameter |
| 3 | 2 | 1 |
| Moderate | Slight | Absent | Ascites |
| > 3 | 2 to 3 | < 2 | Bilirubin (mg/dL) |
| < 2.8 | 2.8 to 3.5 | > 3.5 | Albumin (g/dL) |
| Prothrombin Time |
| >6 | 4 to 6 | 1 to 3 | Seconds over control |
| > 2.3 | 1.8 to 2.3 | < 1.7 | INR |
| Grade 3 to 4 | Grade 1 to 2 | None | Encephalopathy |

Patients were grouped into three categories: class A (well compensated disease, scores 5–6), class B (significant functional compromise, scores 7–9), and class C (decompensated disease, scores 10–15) (Pugh et al., 1973; Lucey et al., 1997).

* Statistical analysis
* Data analysis was assisted by SPSS (Statistical Package for Social Science) software version 16. Nominal and categorical data were expressed as frequency and percentage. Numerical data were expressed as mean, SD, median, minimum, and maximum. The difference between two groups was calculated using unpaired t-test, while the difference between more than two groups was calculated using one-way analysis of variance (ANOVA). Pearson's correlation was used to evaluate correlations between numerical variables. P value less than 0.05 was considered significant (Machin et al., 2007).

Results:

According to the degree of liver dysfunction (assessed by Child Pugh score) patients were divided into 3 groups (classes). It was found that 22 patients (44 %) were in grade A (well-compensated disease), 17 patients (34 %) were in grade B (significant functional compromise) and 11 patients (22 %) were in grade C (decompensated disease).

Table (2) :Comparison of means of IGF-1 level between patient and control groups

|  |  |  |  |
| --- | --- | --- | --- |
|  | Controls (n=50) | Patients (n=50) | P-value |
| Mean ± SD | Median | Min | Max | Mean ± SD | Median | Min | Max |
| IGF-1(ng/ml) | 40.76 ± 4.82 | 40 | 33 | 53 | 26.93 ± 6.33 | 26.58 | 13.7 | 39 | <0.001 |

Comparison of means of IGF-1 level between patient and control groups was shown in table (2). It was found that IGF-1 level was significantly lower in the patients compared to controls.

Table (3): Correlation between IGF-1 level and (serum albumin, total bilirubin, direct bilirubin, PT, INR, AST, ALT, ALP and GGT)

|  |  |
| --- | --- |
| Liver function tests | IGF-1 |
| r | P- value |
| Albumin | 0.456 | 0.001 |
| Total bilirubin | -0.400 | 0.004 |
| Direct bilirubin | -0.401 | 0.004 |
| PT | -0.326 | 0.021 |
| INR | -0.335 | 0.018 |
| AST | -0.366 | 0.009 |
| ALT | 0.098 | 0.499 |
| ALP | -0.013 | 0.927 |
| GGT | -0.134 | 0.355 |

ALP: Alkaline phosphatase - ALT: Alanine aminotransferase - AST: Aspartate aminotransferase - GGT: Gama glutamyltransferase - PT: Prothrombin time - INR: International normalized ratio.

The correlation between serum IGF-1 level and (serum albumin, total bilirubin, direct bilirubin, PT, INR, AST, ALT, ALP and GGT) was illustrated in table (3). It was found that serum IGF-1 level had positive significant correlation with serum albumin and had negative significant correlation with total bilirubin, direct bilirubin, PT, INR, and AST.

Table (4): Comparison of means of IGF-1 level between Child Pugh classes

|  |  |  |
| --- | --- | --- |
|  | Mean ± SD of IGF-1 in different Child Pugh class | P- value |
| Child Pugh A(n=22) | Child Pugh B(n=17) | Child Pugh C(n=11) |
| IGF-1 level | 30.68 ± 5.67ª | 25.60 ± 4.82 ª | 21.47 ± 5.00 ª | <0.001 |

\*: Child Pugh classes sharing the same letter (ª) are significantly different from each others (p<0.05).

Comparison of means of IGF-1 level between Child Pugh classes was demonstrated in table (4). Results showed that IGF-1 level was significantly lower in Child Pugh C compared to Child Pugh B and A. Moreover, IGF-1 level was significantly lower in child Pugh B compared to Child Pugh A.

Table (5): Correlation between anthropometric parameters z scores and serum IGF-1 level

|  |  |
| --- | --- |
| Anthropometric parameters | IGF1 |
| r | P- value |
| Wt z score | 0.119 | 0.411 |
| Ht z score | -0.005 | 0.972 |
| Wt/Ht z score | 0.067 | 0.645 |
| MUAC z score | 0.044 | 0.763 |
| TSFT z score | 0.188 | 0.191 |
| SSFT z score | 0.165 | 0.252 |
| TUAA z score | 0.038 | 0.794 |
| MUAMA z score | -0.098 | 0.497 |
| MUAFA z score | 0.185 | 0.199 |
| AFI z score | 0.265 | 0.063 |

AFI: Arm fat index- Ht: Height- MUAC: Mid upper arm circumference- MUAFA: Mid upper arm fat area- MUAMA: Mid upper arm muscle area-SSFT: Subscapular skinfold thickness-TSFT: Triceps skin-fold thickness-TUAA: Total upper arm area-Wt: Weight-Wt/ht: Weight for height

Correlation between anthropometric parameters and serum IGF-1 level was presented in table (5). Results showed that there was no significant correlation between any of anthropometric parameters and serum IGF-1 level

Table (6) Comparison of means of IGF-1 level between patients with anthropometric parameters z score above and below -2SDS

|  |  |  |
| --- | --- | --- |
|  | Mean ± SD of IGF-1  |  |
| Anthropometric parameters  | Patients with anthropometric parameters z score above -2 SDS | Patients with anthropometric parameters z score below -2 SDS | P- value |
| weight z score | 26.96 ± 6.61 | 26.89 ± 6.09 | 0.970 |
| Height z score | 27.65 ± 6.39 | 26.30 ± 6.33 | 0.459 |
| Wt/Ht z score | 27.38 ± 6.91 | 25.87 ± 4.76 | 0.447 |
| MUAC z score | 27.77 ± 6.98 | 26.41 ± 5.96 | 0.466 |
| TSFT z score | 28.09 ± 6.24 | 26.01 ± 6.36 | 0.253 |
| SSFT z score | 28.02 ± 6.32 | 26.07 ± 6.32 | 0.283 |
| TUAA z score | 28.48 ± 6.97 | 26.26 ± 6.02 | 0.260 |
| MUAMA z score | 26.36 ± 7.06 | 27.58 ± 5.43 | 0.503 |
| MUAFA z score | 27.77 ± 6.33 | 26.15 ± 6.35 | 0.370 |
| AFI z score | 27.23 ± 6.27 | 25.84 ± 6.72 | 0.527 |

AFI: Arm fat index- Ht: Height- MUAC: Mid upper arm circumference- MUAFA: Mid upper arm fat area- MUAMA: Mid upper arm muscle area-SSFT: Subscapular skinfold thickness-TSFT: Triceps skin-fold thickness-TUAA: Total upper arm area-Wt: Weight-Wt/ht: Weight for height

Comparison of means of IGF-1 level between patients with anthropometric parameters z score above and below -2SDS was illustrated in table (6). It was found that there was no significant difference between the 2 groups.

Discussion

In the current study, IGF-1 level was significantly lower in patients compared to controls. Moreover, IGF-I level positively correlated with serum albumin, and negatively correlated with total bilirubin, direct bilirubin, PT, INR and AST. In addition, IGF-1 level was significantly lower in Child Pugh C compared to Child Pugh B and A. Similarly, the IGF-1 level was significantly lower in child Pugh B compared to Child Pugh A. These results come in accordance with Sedlaczek et al., (2003); Vyzantiadis et al., (2003); Wu et al., (2004); Colakoğlu et al., (2007); Dehghani et al., (2012); [Khoshnood](http://www.ncbi.nlm.nih.gov/pubmed?term=Khoshnood%20A%5BAuthor%5D&cauthor=true&cauthor_uid=23599716)  et al., (2013); and [Ronsoni](http://www.ncbi.nlm.nih.gov/pubmed?term=Ronsoni%20MF%5BAuthor%5D&cauthor=true&cauthor_uid=23619263) et al., (2013) who reported similar findings and they mentioned that IGF-1 level negatively correlates to the degree of liver dysfunction and they also concluded that the combined detection of serum IGF-I with Child-Pugh score is more effective in predicting prognosis than Child-Pugh score alone.

The IGF-I deficiency in CLD is thought to result primarily from the reduced synthetic capacity of the hepatocellular mass, combined with a decrease in GH receptors in the cirrhotic liver (Donaghy et al., 2002). The level of bioactive IGF-I is further reduced because of elevated levels of IGFBP-1 and IGFBP -2, which act primarily as blockers of IGF actions. .Another contributing factor is the often reoccurring periods of spontaneous bacterial peritonitis, during which the level of IL-6 is increased. A negative correlation between IL-6 and IGF-I has been reported, possibly owing to IL-6-mediated blockade of the IGF-I production in the liver (Bonefeld and Møller, 2011).

Our results revealed insignificant correlation between any of the nutritional anthropometric parameters and serum level of IGF-1. Moreover, the mean serum level of IGF-1 of patients with anthropometric parameters z score more than -2 SD was not significantly different from patients with theses parameters less than -2 SD. These results are in agreement with Caregaro et al., (1997) and Colakoğlu et al., (2007) who reported that the decrease in IGF-I concentration correlates better with the degree of liver dysfunction rather than the degree of malnutrition.

Conclusion

It could be concluded that IGF-I level was inversely correlated to the degree of liver dysfunction rather than the degree of malnutrition.

Recommendations

In CLD, serum IGF-I can be used as an index of severity of liver disease along with Child Pugh score.

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