Original Article موضوع أصيل

EVALUATION OF INSULIN-LIKE GROWTH FACTOR-1 (IGF-1) IN CHILDREN WITH CHRONIC KIDNEY DISEASES IN BASRA

تقييم عامل النمو المشبه بالأنسولين– 1 (IGF-1) عند الأطفال المصابين بالقصور الكلوي المزمن في البصرة

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ملخص البحث

هدف البحث: يعتبر سوء التغذية وتأخر النمو من المشاكل الشائعة لدى الأطفال المصابين بالقصور الكلوي المزمن، واللذان يساهمان في زيادة المراضة والوفيات المرتبطة بالحالة. يؤدي قصور الكلية المزمن إلى اضطرابات أيضية وهرمونية معقدة، لاسيما في محو (GH - IGF - IGFBP)، والمسؤولة عن العديد من المضاعفات المهمة مثل تأخر النمو الذي يعزى إلى المقاومة النسبية (عدم الحساسية) لتأثيرات هرمون النمو ونقص وظيفة عامل النمو المشبه بالأنسولين، بالإضافة إلى تطور المرض الكلوي. تم إجراء هذه الدراسة لتقييم علاقة مستوى عامل النمو المشبه بالأنسولين-1 (IGF-1) مع الحالة التغذوية وبعض المتغيرات الأخرى عند الأطفال الذين يعانون من القصور الكلوي المزمن.

طرق البحث: تم اختيار 41 مريضاً من مرضى القصور الكلوي المزمن و50 من الأطفال الأصحاء كمجموعة شاهد، خلال الفترة بين 1 من تشرين الأول 2015 وحتى 15 آذار 2016. تمت مراجعة السجلات الطبية لجميع المرضى وتم جمع المعلومات التالية: تاريخ الميلاد، الجنس، العمر، بداية تشخيص المرض، الأعراض الملاحظة، طريقة العلاج المتبعة (العلاج الدوائي، التحال الدموي، التحال البريتواني المتنقل المستمر)، ونوعية التغذية. تم إجراء تقييم االحالة التغذوية من خلال التقييم السريري لعلامات سوء التغذية وبيانات القياسات البشرية (الأنثروبومترية) على النحو التالي: (الوزن بالنسبة للعمر، الطول بالنسبة للعمر، محيط منتصف الذراع، مشعر كتلة الجسم BMI)، حيث تم تطبيقها على مخططات النمو المناسبة. تم أيضاً إجراء الفحوصات التالية: مستوى عامل النمو المشبه بالأنسولين-1، وظائف الكلية، معايرة شوارد الدم ومستوى الخضاب الدموي (الهيموغلوبين). كذلك تم تقييم شدة القصور الكلوي المزمن من خلال حساب معدل الرشح الكبيبي لجميع المرضى.

النتائج: من مجموع 41 مريضاً يعانون من القصور الكلوي المزمن فقد كان عدد الذكور 29 (بنسبة 70.7%) والإناث 12 (بنسبة 29.3%)، كما تم تشخيص 51.3% من الحالات بعد عمر 5 سنوات، مع وجود نسبة مرتفعة من المرضى الموضوعين على العلاج الدوائي (27 مريضاً بنسبة 65.9%)، مقابل نسبة أقل (8 مرضى فقط بنسبة 19.5%) موضوعين على التحال البريتواني المتنقل المستمر، ونسبة أقل من المرضى الموضوعين على التحال الدموي (6 مرضى بنسبة 14.6%). أظهرت نسبة الرسوب في المدرسة ارتفاعاً ملحوظاً لدى الأطفال المصابين بالقصور الكلوي المزمن بالمقارن مع مجموعة الشاهد (41.4% مقابل 8% على الترتيب)، كما أن أكثر من 50% من المرضى ينتسبون لآباء يفتقرون للتعليم (حيث كانت الفوارق المسجلة هامة إحصائياً). سجل سوء التغذية بشكلٍ ملحوظ لدى 63.4% من مرضى القصور الكلوي المزمن (26 مريضاً من أصل 41)، حيث كان منحني النمو أقل من 5%. كذلك لوحظ عدم كفاية الوارد الغذائي عند 73.1% من مرضى سوء التغذية وعند 33.3% من حالات عدم وجود سوء التغذية. لوحظ انخفاض مستوى عامل النمو المشبه الأنسولين-1 بشكلٍ ملحوظ لدى المرضى الذين يعانون من القصور الكلوي المزمن بالمقارنة مع مجموعة الشاهد (91.12±71 نانوغرام/مل مقابل 279±53.2 نانوغرام/مل، على الترتيب)، وعند مرضى سوء التغذية بالمقارنة مع حالات عدم وجود سوء تغذية (47.11±19 نانوغرام/مل مقابل 167±65.6 نانوغرام/مل، على الترتيب). لم يلاحظ وجود تأثير واضح لنمط العلاج أو شدة المرض على الحالة التغذوية للمرضى الذين شملتهم الدراسة.

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الاستنتاجات: يشكل سوء التغذية لدى مرضى القصور الكلوي مشكلة كبيرة يجب تشخيصها في وقت مبكر. يمكن لإجراء المزيد من الدراسات المستقبلية حول العلاج باستخدام مشابهات عامل النمو المشبه بالأنسولين-1 أن يساعد في تحسين تدبير حالة فشل النمو عند هؤلاء المرضى.

ABSTRACT

Objective: *Malnutrition and growth delay are common in children with chronic kidney diseases and associated with a greater risk of morbidity and mortality. Chronic kidney diseases results in complex metabolic and hormonal disturbances, particularly in the (GH-IGF-IGFBP) axis; responsible for many important complications, such as growth retardation which is due to a relative growth hormone insensitivity and functional IGF deficiency as well as disease progression. A case control study has been carried out to assess level of insulin like growth factor-1 (ILGF-1) in children with chronic kidney disease in relation to their nutritional status and some selected patients' variables*

Methods: *Forty one patients with chronic kidney diseases and 50 healthy children as a control group were selected from 1st of October 2015 till 15th March 2016. The medical records were reviewed for all patients and the following information was collected: birth date, sex, age, onset of diagnosis of kidney diseases, presenting symptoms, modality of treatment (medical therapy, hemodialysis, continuous ambulatory peritoneal dialysis) and dietary history (three non-consecutive 24 hours food record, food restriction and supplements). Nutritional assessment was conducted by clinical evaluation for signs of malnutrition and anthropometric data such as (weight for age, height for age, mid upper arm circumferences and body mass index) were applied on appropriate growth charts. Investigations done included: insulin like growth factor-1, renal function tests, serum electrolytes, and hemoglobin. The severity of kidney diseases was assessed by calculation of glomerular filtration rate (GFR) for all patients.*

Results: *Out of 41 patients with chronic kidney diseases; 29 (70.7%) were males and 12 (29.3%) were females, 51.3% are diagnosed after the age of 5 years, with higher frequency of patients on conservative treatment 27 (65.9%), whereas only 8 (19.5%) were on continuous ambulatory peritoneal dialysis with less frequency of patients on hemodialysis (6 patients, 14.6%). Higher frequency of school failure reported in children with chronic kidney diseases than control (41.4 and 8%, respectively), and more than 50% belong to illiterate parents with statistically significant results. Malnutrition was significantly recorded in 63.4% patients with chronic kidney diseases (41 patients out of 26); their growth parameters were below 5th percentile. Significantly inadequate dietary intake was reported in 73.1% of patients with malnutrition, and in 33.3% of patients without malnutrition. Significantly low mean level of insulin like growth factor-1 recorded in patients with chronic kidney disease than control group (91.12±71 and 279±53.2, respectively), and in malnourished patients than those without malnutrition (47.11±19 and 167±65.6, respectively), p-value was 0.0001. Modality of treatment and severity of chronic kidney diseases seem to have no obvious effect on nutritional status of studied patients.*

Conclusions: *Malnutrition in children with chronic kidney diseases is a major problem; essential to be recognized as early as possible, further studies on treatment with insulin like growth factor-1 analogues could provide an opportunity to improve management of growth failure of such patients.*

INTRODUCTION

Infants and young children have high energy demands and low levels of energy stores, therefore; they are especially vulnerable to nutritional imbalances which will prevent a normal growth velocity. Malnutrition remains a major problem in patients with chronic kidney diseases (CKD), adversely affecting functional activity and patients 'quality of life. Factors that responsible for malnutrition in chronic kidney disease include; disorder in protein, carbohydrate and lipid metabolism, chronic inflammation, oxidative stress, hormonal derangement, metabolic acidosis, dialysis related problem and side effect of medication.[1]

In children with CKD, growth has been linked to the free insulin like growth factor-1 (IGF-I) levels.[2] The

IGF-I circulates in serum as a 150 kD complex trimer which includes IGF-I, IGF binding protein (IGFBP), and acid labile subunit (ALS). In CKD patients a decreased renal clearance of IGFBP is observed, which leads to an excess of IGFBP-1 in the circulation and the concomitant decrease in the levels of bioactive IGF-I, the decrease is correlated with the degree of renal failure.[3]

METHODS

This is case-control study has been carried out to evaluate IGF-1 level, and assess the nutritional status of 41 patients, aged 3-14 years; (29 males and 12 females) with chronic kidney diseases (CKD) who were admitted to Basra General Hospital, dialysis unit and pediatric wards or those who were visited pediatric emergency room.

Fifty apparently healthy children, age and sex matched, were selected as a control group.

The enrolled patients are those who have kidney damage; which defined by the presence of any structural or functional abnormality involving pathological, laboratory or imaging finding for >3 months or patients with GFR <60 ml/min/1.73 m^2 more than or equal to 3 months of illness.[4]

Growth parameters for CKD patients					
Percentile	WFA No. (%)	HFA No. (%)	MUAC No. (%)	BMI No. (%)	p-value
<5th	29 (70.7)	28 (68.3)	26 (63.4)	26 (63.4)	0.0001
≥5th	12 (29.3)	13 (31.7)	15 (36.6)	15 (36.6)	
Growth parameters for control					
10-25th	13	12	19	14	0.0001
50-75th	37	37	30	31	
75-90th	0	1	1	5	

Table 1. Growth parameters in children with CKD and control.

Variables		CKD with malnutrition		CKD without malnutrition		p-value
		No.	%	No.	%	
Age onset of diagnosis (years)	1-5	13	50	7	46.7	0.4
	5-10	6	23	6	40	
	10-14	7	27	2	13.3	
Duration of treatment (years)	1-3	10	38.4	12	80	0.01
	>4	16	61.6	3	20	
Modality of treatment	Conservative	17	65.4	10	66.7	0.41
	Hemodialysis	5	19.2	1	6.6	
	CAPD	4	15.4	4	26.7	
Frequency of dialysis	Thrice/week.	4	15.4	2	13.3	0.8
	Twice/week.	1	3.8	1	6.6	
	Three/day (CAPD)	4	15.4	2	13.3	
Complications history	Seizure	2	7.7	2	13.3	0.68
	CVA	2	7.7	0	0.0	
	HF	3	11.5	1	6.7	
No complications		19	73.1	12	80	
Total (41)		26	63.4	15	36.6	

Table 2. Nutritional status of children with CKD in relation to selected patients' variables.

Variables		CKD with malnutrition		CKD without malnutrition		p-value
		No.	%	No.	%	
Sex	Males	18	69.2	11	73.3	0.7
	females	8	30.8	4	26.7	
Educational level	Not attend school	9	34.6	1	6.7	0.1
Patients	Failure	10	38.5	7	46.6	
	Primary	5	19.2	6	40	
	Secondary	2	7.7	1	6.7	
Mothers	Illiterate	19	73.1	3	20	0.04
	Primary	1	3.8	5	33.33	
	Secondary	4	15.4	5	33.33	
	Academic	2	7.7	2	13.34	
Fathers	Illiterate	19	73.1	2	13.3	0.03
	Primary	1	3.8	3	20	
	Secondary	2	7.7	7	46.7	
	Academic	4	15.4	3	20	
Family size	Small	5	19.2	2	13.3	0.5
	Large	21	80.8	13	86.7	
Total (41)		26	100	15	100	

Table 3. Relation of nutritional status of patients with CKD to parents' related variables.

Dietary history		CKD patients with malnutrition		CKD patients without malnutrition		p-value
		No.	%	No.	%	
Dietary intake	Adequate	7	26.9	10	66.7	0.0001
	Inadequate	19	73.1	5	33.3	
Food restriction	Yes	14	53.8	6	40	0.29
	No	12	46.2	9	60	
Total		26	100	15	100	

Table 4. Relation of dietary history to nutritional status of children with CKD.

Variables		CKD with malnutrition		CKD without malnutrition		Total No. (%)	p-value
		No.	%	No.	%		
GFR stages	2	0	0.0	2	13.4	2 (4.9)	0.101
	3	12	46.2	7	46.6	19 (46.3)	
	4	8	30.8	4	26.7	12 (29.3)	
	5	6	23	2	13.3	8 (19.5)	
Modality of treatment	Conservative	17	65.4	10	66.7	27 (65.9)	0.41
	Hemodialysis	5	19.2	1	6.7	6 (14.6)	
	CAPD	4	15.4	4	26.6	8 (19.5)	
Total		26	63.4	15	36.6	41 (100)	

Table 5. Relation of nutritional status of children with CKD and modality of treatment and GFR.

A special questionnaire was designed for the purpose of the study. The following information was taken: identity of the patients, presenting symptoms, modality of treatment, dietary history, family size and education level. Insulin like growth factor, hemoglobin, blood urea, serum creatinine, serum electrolytes and total iron binding capacity (TIBC) were done for all patients and control group. Approval from ethical committee was obtained and informed consent for enrollment in the study was taken from the families, besides patients' medical records were reviewed.

Anthropometric measurements were assessed for all children and applied to appropriate charts. Weight (dry weight) had been measured midweek for patients with continuous ambulatory peritoneal dialysis (CAPD), and 1-2 hours after hemodialysis.[5] Patients were considered as malnutrition when mid-upper arm circumference, weight for height and body mass index are below 5th percentile.[6] Glomerular filtration rate (GFR) calculated according Schwartz formula.[7] Dietary intake determined by using 3 non-consecutive 2, 4-hours dietary recalls.[8] Data were analysed using SPSS software version 20.

RESULTS

Nutritional status of studied children: Malnutrition has been considered in 63.4% of children with CKD, the most significantly affected parameter was BMI <5th percentile. On the other hand, all growth parameters (WFA, HFA and MUAC) were <5th percentile than control group with statistically significant result, Table 1.

Relation of selected patients' variables with nutritional status: Table 2 shows significant association of malnutrition in CKD patients with longer duration of treatment (>4 years). While age onset of diagnosis (years), duration of treatment (years), modality of treatment, frequency of dialysis and complication history had no association with poor nutrition.

Relation of educational level and family size in children with CKD and nutritional status: Table 3 shows that the educational level of parents of malnourished patients with CKD are significantly lower than CKD patients without malnutrition.

Variables		Mean±SD IGF-1 (ng/ml)		p-value
		Control	CKD patients	
Mean±SD IGF-1 (ng/ml)		91.12±71.9	279.1 ±53.23	0.0001
		CKD with malnutrition	CKD without malnutrition	
Age (years)	3-5 (8 patients)	31.6±8.65	160.3 ±69	
	5-10 (15 patients)	35.79±12.3	190.6±56	
	10-14 (18 patients)	59.4±17.1	151.2±77.4	
Total (41)		47.11±19	167.4±65.6	

Table 6. Level of IGF-1 in CKD patients and control group in relation to their nutritional status.

Variables	Odd ratio	CI		p-value
		Lower	upper	
Dietary intake	7.02	1.35	36.36	0.02
Dietary supplements	1.39	1.02	1.90	0.03
Father education	5.02	1.02	24.63	0.04
Mother education	0.20	0.04	0.85	0.03
Sex	1.38	0.24	7.97	0.71
Modality of treatment	0.79	0.48	1.31	0.36
Family size	0.70	0.16	2.95	0.63
Duration of treatment	0.80	0.23	2.73	0.72

Table 7. Logistic regression of selected variables.

Glomerular filtration rate (GFR) and modality of treatment in patients with CKD: Patients with GFR stage 3 are more liable to have malnutrition than other stages, and 17 (65.4%) of patient on conservative treatments have malnutrition, as shown in Table 4.

Relation of dietary history to nutritional status: As shown in Table 5; CKD patients with malnutrition have significantly inadequate dietary intake than patients without malnutrition (73.1% and 33.3%, respectively), p-value <0.05.

Insulin like growth factor-1 (IGF-1) in studied children: Table 6 shows significantly low mean IGF-1 level in children with CKD than in control group (91.12±71.9 versus 279.1±53.23, respectively); as well as low IGF-1 in CKD patients with malnutrition than those without malnutrition, with statistically significant result.

Logistic regression of selected variables: Patients with history of inadequate dietary intake and those belong to illiterate parents were most likely to develop malnutrition with significant result. Other variables like age, sex, family size, modality of treatment and duration of treatment have no effect on nutritional status of patients with CKD, as shown in Table 7.

DISCUSSION

Chronic kidney diseases (CKD) in pediatric population has become an important issue; affected children display serious medical complication as well as increased mortality. Malnutrition is a common and significant clinical problem in children with CKD in which effect of nutritional status on general wellbeing of patients.[9] The precise incidence of CKD in Iraqi children is still lacking, and no data available in Basra even in many countries. The current study assess 41 patients with CKD over a period of 5 months; in comparison to a study carried out in Baghdad by Nariman et al, who retrospectively studied 50 patients from 2002-2007,[10] and in Saudi by Jameela et al in 2006.[11]

Nutritional evaluation of patients with CKD reveals that 63% are malnutrition, which seem higher than other levels reports in Baghdad by Nariman et al (24%),[10] Egypt by Noushira E et al,[12] North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) annual reports (37%), and in Chile by Salas P et al (50%).[13] There are many factors implicated in the pathogenesis of growth failure in CKD such as anemia, metabolic acidosis, chronic inflammation, inadequate nutritional intake and food restriction.

Higher frequency of inadequate dietary intake reported in malnourished CKD patients; mainly due to improper food intake and restriction; patients with CKD should receive at least 80% of age appropriate dietary recommendation to achieve a normal growth rate.[13]

The severity of kidney failure and modality of treatment did not significantly influence the severity of growth impairment (which indicate that nutrition status deterioration may begin at even earlier stages); similar results concluded by Apostolou et al.[14]

Growth retardation recorded in children with longer duration of kidney disease in cohort study in Turky by Sozeri B et al; was found to be associated with short stature,[9] this conclusion is consistent with the current study, where short stature recorded in 68.3%.

Significantly low level of IGF-1 in CKD patients than control group and in patients with malnutrition reported in current study; this is in agreement with a study done in 2007 by Derakhshan et al.[15] Low level of free IGF-1 is multi-factorial due to decreased in insulin-like growth factor binding proteins and increase in other carrier proteins and growth hormone resistance.[16]

Educational level of patients with CKD is an important factor to be determined for CKD patients' nutritional status, whom belong to illiterate parents; accounts (73.1%) of CKD patients with malnutrition, this is agreement with study carried out by Arlene et al in 2010;[17] because the burden of care for children with CKD is the responsibility of the family and require attention includes self-catheterization several time/day, fluid and dietary restriction, blood pressure monitoring and erythropoietin injection; so illiterate parents with

poor compliance to the treatment and no education about CKD treatment, dialysis, associated dietary problems regards as predictor factor for malnutrition.

CONCLUSIONS

Approximately 63% of studied children with chronic kidney disease consider as malnourished according to weight for age, height for age, body mass index and mid upper arm circumferences below 5th percentile. Higher frequency of school failure recorded in children with chronic kidney disease than control group, and more than 50% of them belonged to illiterate parents. Inadequate calories intake recorded in two third of patients with malnutrition. Modality of treatment and severity of chronic kidney disease seem to have no obvious effect on nutritional status of studied patients. Significantly lower level of IGF-1 reported in CKD patients than control group, and in those with and without malnutrition. The predictable risk for malnutrition in patients with chronic kidney disease is food restriction and those belong to illiterate parents.

RECOMMENDATIONS

Growth failure remains a major problem in children with chronic kidney diseases, it is essential to be recognized as early as possible. The nutritional status in these children require frequent evaluation and dietician counselling. Screening for IGF-1 has its promising effect for monitoring nutritional status and growth of children with chronic kidney diseases.

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