



Assessment of Cystatin-C level in Newly Diagnosed Iraqi Children with Nephritic Syndrome

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Abstract

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BACKGROUND: Nephritic syndrome (NS) is a common kidney disease in children that causes protein leakage from the blood into the urine due to glomerular injury.

AIM: The aim of this research was to determine the level of Cystatin-C (CysC) and other biochemical parameters in newly diagnosed NS children in Iraq.

PATIENTS AND METHODS: Ninety Iraqi children divided into: 50 children with newly diagnosed NS (28 boys and 22 girls) aged between (4 and 16) years, and 40 healthy control children (20 boys and 20 girls) aged between (5 and 16) years, who were attending Al-Yarmouk Teaching Hospital, Baghdad.

RESULTS: There was a significant increase in blood urea, serum total cholesterol (S.TC), and serum low density lipoprotein (S.LDL) and a significant decreased of serum creatinine (S. creatinine), protein/creatinine ratio, serum total bilirubin, serum albumin, and serum high density lipoprotein, while a highly significant increased ($p < 0.001$) of CysC levels in children with newly diagnosed NS when compared with control group. A significant positive correlation between CysC level versus systolic blood pressure, body mass index, diastolic blood pressure, S.TC, S. LDL cholesterol (S.LDL-C), S. Total Bilirubin, S. Albumin, S. Total protein, and B. urea, while a significant negative correlation was found between CysC level versus serum low density lipoprotein cholesterol and estimated glomerular filtration rate in children with newly diagnosed NS.

CONCLUSION: It may come to the conclusion that CysC can be the best predictor of overall efficacy than creatinine and in the diagnosis of any damage to the kidney in children with NS.

Introduction

Nephritic syndrome (NS) is a common kidney condition in children that results in protein leakage from the blood into the urine as a result of glomeruli dysfunction [1]. The classic concept is proteinuria in the nephrotic range (40 mg/m²/h or urine (protein/creatinine ratio) of 200 mg/mL protein on a dipstick of urine) [2]. Childhood NS can be congenital, appearing during the first 3 months of life; moreover, in these babies, a genetic defect affecting either the podocyte or the glomerular basement membrane is usually present, though it can sometimes be attributed to congenital infections including cytomegalovirus [3]. Nephrotic syndrome can be caused by a variety of underlying etiologies (glomerular diseases, vasculitides, bacteria, toxins, cancer, and genetic mutations) and most often, unexplained causes [4], [5].

Cystatin-C (CysC), a low molecular weight (thirteen-kDa) protein, is generally formed by all nucleated cells that is filtered freely by the renal glomeruli and reabsorbed in the proximal tubule. In healthy people, age and muscle mass have no effect

on CysC levels. Urinary incontinence CysC is a protein that indicates renal tubular dysfunction [6], [7]. CysC is a cysteine protease inhibitor secreted into the bloodstream by human cells. Meanwhile, applying the CysC-based equation to the risk classification for death, cardiovascular diseases, along with end-stage-renal disease has been demonstrated to improve overall risk classification [5], [8], [9]. Different equations for estimating chronic kidney disease depended on creatinine or CysC measures, on the other hand, appear to behave differently in high-risk and low-risk populations and subgroups, such as older adults or diabetes patients [9]. For the diagnosis of kidney injury, serum CysC has been proposed as a new biomarker. Serum CysC is a better marker of reduced glomerular filtration rate (GFR) than serum creatinine, according to the several studies [10], [11], [12]. Other characteristics include being present in steady quantities in the plasma, not being secreted by tubular cells, as well as being less affected by the non-renal factors: For example, muscles mass, sex, age, and analytical interfering material during determination when compared to creatinine [13], [14]. The rapid and accurate particle enhanced turbidimetric or nephelometric immunoassays (PETIA and PENIA) are used to calculate CysC levels [15].

The aim of this study was to determine the level of CysC and other biochemical parameters in newly diagnosed NS children in Iraq.

Materials and Methods

Subjects and methods

Ninety Iraqi children divided into: 50 children with newly diagnosed NS (28 boys and 22 girls) aged between (4 and 16) years, and 40 healthy control children (20 boys and 20 girls) aged between (5 and 16) years, who were attending Al-Yarmouk Teaching Hospital, Baghdad, from December 2019 to September 2020. Data were collected from all patients include sex, age, blood pressure, and body mass index (BMI). Serum fasting blood sugar (S.FBS), serum total protein (S. Total protein), serum albumin (S. Albumin), serum bilirubin (S. Bilirubin), lipid profile (serum total cholesterol [S.TC], serum triglyceride [S.TG], and serum high density lipoprotein [S.HDL-C]), blood urea (B. urea), and serum creatinine (S. creatinine) were estimated using automated kenza Tx 240 instrumental. Furthermore, protein creatinine ratio was calculated. The estimated GFR (eGFR) was determined by equation dependent on patients' sex [16]. In addition, CysC concentrations were measured by enzyme-linked immunoassay (CUSABIO kit: CHINA, catalog. E08384h).

Statistical analysis

The results of this study are presented as mean \pm SD. The importance of a difference in mean values between two groups was determined using the Student-t test ($p < 0.05$ was considered significant).

Results

Table 1 shows the means of different parameters between children with newly diagnosed NS and control group. There was a significant decrease in weight, BMI, and systolic blood pressure (SBP) in children with newly diagnosed NS relative to control group, while no significant difference in age, height, and diastolic blood pressure (DBP) between children with newly diagnosed NS and control group.

Characteristic biochemical parameters in children and control were summarized in Table 2. There was no significant deference of S.FBS and S.TG between children with newly diagnosed NS and control group, while a highly significant increased ($p < 0.001$)

Table 1: Characteristics of anthropometric measurements of children with newly diagnosed nephritic syndrome and control group

Parameters	Nephritic syndrome (n = 50)	Control (n = 40)	p-value
Age (years)	12.80 \pm 4.31	11.46 \pm 6.18	0.41 (NS)
Gender (Boys/Girls) n.	28/22	20/20	-
Weight (kg)	12.25 \pm 2.33	20.61 \pm 2.78	0.05*
Height (cm)	99.40 \pm 5.30	120.0 \pm 6.18	0.06 (NS)
BMI (kg/m ²)	14.10 \pm 2.42	18.74 \pm 2.50	0.05*
SBP (mmHg)	95.0 \pm 1.00	110.81 \pm 1.18	0.05*
DBP (mmHg)	60.0 \pm 5.03	70.50 \pm 5.00	0.07 (NS)

NS: No significance differences, * $p < 0.05$ is significant. SBP: Systolic blood pressure, DBP: Diastolic blood pressure, BMI: Body mass index.

of S.TC and S.LDL-C ($p < 0.01$) between children with newly diagnosed NS when compared with control group. Furthermore, it seems in Table 2 that there is a significant decreased ($p < 0.05$) of S.HDL-C in children with newly diagnosed NS relative to control group.

Table 2: Biochemical characteristics measurements between children with newly diagnosed nephritic syndrome and control group

Parameters	Nephritic syndrome (n = 50)	Control (n = 40)	p-value
S.FBS (mg/ml)	84.30 \pm 5.20	72.50 \pm 6.21	0.33 (NS)
S.TC (mg/ml)	320.32 \pm 18.61	142.3 \pm 21.60	0.001**
S.TG (mg/ml)	100.20 \pm 10.22	90.0 \pm 5.50	0.106 (NS)
S.HDL-C (mg/ml)	40.25 \pm 5.62	55.55 \pm 3.27	0.05*
S.LDL-C (mg/ml)	109.10 \pm 8.12	70.0 \pm 7.12	0.01**

NS: No significance differences, * $p < 0.05$ is significant, ** $p < 0.01$ is highly statistically significant.

TC: Total cholesterol, TG: Triglyceride, FBS: Fasting blood sugar, LDL: Low-density lipoprotein cholesterol, HDL: High-density lipoprotein cholesterol.

As shown in Table 3, a significant decreased ($p < 0.05$) in S. Total bilirubin, while a highly significant decreased ($p < 0.001$) in S. Albumin and S. Total Protein in children with newly diagnosed NS when compared with control group.

Table 3: S. total bilirubin, S. albumin and S. total protein measurements between children with newly diagnosed nephritic syndrome and control group

Parameters	Nephritic syndrome (n = 50)	Control (n = 40)	p-value
S. Total Bilirubin (mg/ml)	0.30 \pm 0.21	1.20 \pm 0.60	0.05*
S. Albumin (g/L)	17.32 \pm 3.61	38.3 \pm 4.60	0.001**
S. Total Protein (g/L)	31.25 \pm 3.33	70.81 \pm 8.11	0.001**

* $p < 0.05$ is significant. ** $p < 0.01$ is highly statistically significant.

There was a significant increased ($p < 0.05$) in B. urea, while a significant decreased ($p < 0.05$) of S. creatinine and protein/creatinine ratio in children with newly diagnosed NS when compared with control group. A highly significant decreased ($p < 0.001$) of eGFR in children with newly diagnosed NS when compared with control group (Table 4).

Table 4: B. urea, S. creatinine, protein/creatinine ratio and eGFR measurements between children with newly diagnosed nephritic syndrome and control group

Parameters	Nephritic syndrome (n = 50)	Control (n = 40)	p-value
B. urea (mg/ml)	45.30 \pm 2.22	25.10 \pm 3.11	0.05*
S. creatinine (mg/ml)	0.4 \pm 0.31	0.81 \pm 0.10	0.05*
Protein/creatinine Ratio	0.11 \pm 0.07	0.62 \pm 0.30	0.05*
eGFR	36.55 \pm 3.32	93.21 \pm 6.72	0.001**

* $p < 0.05$ is significant. ** $p < 0.01$ is highly statistically significant. eGFR: Estimated glomerular filtration rate.

As shown in Table 5, there was a highly significant increased ($p < 0.001$) of CysC levels in children with newly diagnosed NS when compared with control group.

Table 5: CysC levels between children with newly diagnosed nephritic syndrome and control group

Parameter	Nephritic syndrome (n = 50)	Control (n = 40)	p-value
CysC (ng/ml)	34.25 \pm 3.92	23.66 \pm 3.04	0.001**

** $p < 0.01$ is highly statistically significant. CysC: Cystatin-C.

Table 6 shows a significant positive correlation between CysC level versus SBP, BMI, DBP, S.TC, S.LDL-C, S. Total Bilirubin, S. Albumin, S. Total protein, and B. urea, while a significant negative correlation was found between CysC level versus S.HDL-C and eGFR in children with newly diagnosed NS.

Table 6: Correlation coefficient between CysC level and all parameters

Parameters	Correlation coefficient (r)
CysC versus Age	0.133 (NS)
CysC versus BMI	0.322*
CysC versus SBP	0.287*
CysC versus DBP	0.301*
CysC versus S.FBG	0.141 (NS)
CysC versus S.TC	0.62**
CysC versus S.TG	0.432*
CysC versus S.HDL-C	-0.305*
CysC versus S.LDL-C	0.358*
CysC versus S. Total Bilirubin	0.361*
CysC versus S. Albumin	0.324*
CysC versus S. Total protein	0.311*
CysC versus B. urea	0.391*
CysC versus S. Creatinine	0.106 (NS)
CysC versus eGFR	-0.588**

NS: No significance differences. *Correlation is significant at the 0.05 level. **Correlation is significant at the 0.01 level. SBP: Systolic blood pressure, DBP: Diastolic blood pressure, BMI: Body mass index, TC: Total cholesterol, TG: Triglyceride, FBS: Fasting blood sugar, LDL: Low-density lipoprotein cholesterol, HDL: High-density lipoprotein cholesterol, eGFR: Estimated glomerular filtration rate, CysC: Cystatin-C.

Discussion

This is the first study to look at CysC levels in children with renal disease in Iraq. Unlike adults, children with renal disease may be difficult to detect early because they may have few symptoms. Kidney damage normally occurs before improvements in renal function, as albuminuria occurs before any decrease in eGFR [17]. Albuminuria is the standard biomarker for kidney damage, it may be absent in other forms of kidney damage such as tubulointerstitial disease and hypertensive kidney disease [18]. Some kidney disorders are inherited, such as Alport syndrome, a hereditary progressive nephropathy characterized by lamellation and fracturing of the glomerular basement membrane, as well as sensor neural defects leading to hearing loss and ocular defects. Hematuria and later development to renal failure and polygenic kidney disorders are signs of it in early childhood [19], [20].

There was a significant decrease in weight, BMI, and SBP, while no significant difference in age, high, and DBP between children with newly diagnosed NS and control group, and this is agreement with [21], [22]. A highly significant increased ($p < 0.001$) of TC between children with newly diagnosed NS when compared with control group. Furthermore, it seems that there is a significant decreased ($p < 0.05$) of HDL-C in children with newly diagnosed NS relative to control group, and this is agreement with Mohamed *et al.* [23]. Elevation of S. TC, low-density lipoprotein cholesterol, and decreased HDL-C are the most important lipid disorder in NS and can develop the disorder progresses. Nephrotic hyperlipidemia is a disease with

a complicated pathophysiology. The general consensus is that hepatic lipid and Apo lipoprotein synthesis is increased, whereas chylomicron and VLDL clearance are decreased. The exact role of elevated lipogenesis and decreased lipid catabolism in hyperlipidemia, as well as their links to loss protein in urine and hypoalbuminemia, is unknown [24].

As shown in this study, there was a significant decreased ($p < 0.05$) in S. total bilirubin and a highly significant decreased ($p < 0.001$) of S. Albumin and S. Total Protein in children with newly diagnosed NS when compared with control group, this result is agreement with the following studies [25], [26]. Reduced albumin output (rare), elevated albumin loss through the kidneys, skin, gastrointestinal tract, or extravascular space, increased albumin catabolism, or a combination of two or more of these mechanisms may all lead to hypoalbuminemia [27]. Albumin performs a variety of functions in the human body. Maintaining oncotic pressure inside the vascular compartments, which prevents fluid leakage into the extravascular spaces, is one of the most important [28], [29]. Because to a fractionally higher free bilirubin, bilirubin brings an elevated risk of kernicterus; such babies should be treated vigorously with phototherapy if the diagnosis is made early enough. Statins, which are commonly used to treat hyperlipidemia and hypercholesterolemia, do not yet have a well-established position in the "Congenital Nephrotic Syndrome" [30]. Microalbuminuria is a sign of harm to the basement membrane of the glomerulus, as well as vascular and endothelial injury. The previous researches have revealed its significance as an independent predictor of renal disease progression [20], [31]. Increased intraglomerular hydrostatic pressure and increasing GFR are recognized major hemodynamic disturbances that are responsible for kidney dysfunction in children, according to the Mieczyslaw *et al.* [25], glomerular sclerosis is the most common histopathologic characteristic of glomerulopathy, which is caused by glomerular hyperfiltration and hypertrophy.

The previous studies [32], [33], [34] showed a highly significant increased ($p < 0.001$) of CysC levels in children with newly diagnosed NS when compared with control group, and this is agreement with our results. A significant positive correlation between CysC level vs. BMI, SBP, DBP, TC, LDL-C, S. Total bilirubin, S. Albumin, S. Total protein and B. urea, while a significant negative correlation was found between CysC level vs. HDL-C and eGFR in children with newly diagnosed NS [35], [36]. Marco Zaffanello *et al.* [37] found negative correlation between serum CysC and GFR, but serum CysC was not correlated with serum creatinine. According to the Salman *et al.* [38], this finding indicates that CysC is a better biomarker than creatinine for detecting the negative effects of dyslipidemia on renal function in NS infants.

Conclusion

It may come to the conclusion that increased CysC in newly diagnosed children with NS and a positive correlation between CysC versus S.TC, S. Total bilirubin, S. Albumin, S. Total protein and B. urea, also, a significant negative correlation was found with S.HDL-C and the eGFR in children with newly diagnosed NS. This gives us an idea that CysC can be the best predictor of overall efficacy than creatinine and in the diagnosis of any damage to the kidney in children with NS.

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