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Comparison between serum nephrin and microalbuminuria as biomarkers for sickle cell nephropathy

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Sickle cell anemia is the most common monogenic blood disorder. The most common genotype is homozygous hemoglobin SS. Damage to red blood cells occurs due to changes in shape and function of the hemoglobin molecule inside it. This results in hemolytic anemia and the blockade of small blood vessels, which lead to vaso-occlusion and end organ failure. Sickle cell disease significantly alters renal structure and function and causes diverse renal diseases. To evaluate the validity of serum nephrin as a biomarker of sickle nephropathy and compare its sensitivity versus urinary microalbuminuria in the early detection of sickle cell nephropathy. This case control study was conducted on sixty patients suffering from sickle cell disease, 10 of them were diagnosed as sickle nephropathy, in addition to sixty apparently healthy children as a control group. Laboratory tests were hemoglobin electrophoresis, urinary microalbumin, serum ferritin, urea and creatinine. The glomerular filtration rate was estimated and serum nephrin was measured using enzyme-linked immunosorbent assay. Among children with sickle cell anemia, 16.6% (10 patients) had sickle nephropathy diagnosed with elevated kidney function and low glomerular filtration rate. Liver and kidney function were significantly higher in cases with nephropathy than cases without nephropathy, while glomerular filtration rate was significantly lower in cases with nephropathy than cases without nephropathy. Serum nephrin was significantly higher in patients with nephropathy than patients without nephropathy versus non-significant difference regarding microalbuminuria level. The cutoff point for nephrin to diagnose sickle cell nephropathy was > 13 ng/mL versus 29.5 mg/dL for urinary microalbumin. Serum nephrin could be a valuable biomarker in early diagnosis of nephropathy in patients with sickle cell anemia.

Key words: *sickle cell anemia, serum nephrin, microalbumin, sickle nephropathy*

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Sickle cell disease (SCD) is caused by a single base pair mutation (Glu6Val) in the globin gene. The most common genotype is homozygous hemoglobin SS (HbSS), and common heterozygous conditions are hemoglobin sickle beta zero thalassemia, hemoglobin sickle beta plus thalassemia (hemoglobin sickle beta plus thalassemia), and hemoglobin SCD [1]. SCD is more prevalent in Sub-Saharan Africa, South Asia, the Middle East, and the Mediterranean. The prevalence of SCD in the United States is expected to be roughly 100,000 and is projected to grow [2]. SCD is present in Egypt especially in the Oases where the carrier rate ranges from 9 to 22% [3]. The low partial pressure of oxygen (10 to 35 mmHg), acidosis, and high osmolarity contribute to hemoglobin S tetramerization and consequent sickling of the erythrocytes resulting in renal problems in SCD which come from the occluded veins (vasa recta) in the renal medulla. Sickle cell nephropathy cases exhibit microinfarcts and ischemia damage because of repeated sickling cycles. This results in chronic microvascular illness [4].

The activation of hypoxia-inducible factor 1 alpha, endothelin-1 mRNA expression and reduced nitric oxide – which promotes an increase in reactive oxygen species and vasoconstriction by constricting blood vessels – contribute to the cycles of chronic medullary hypoxia [5]. Proteinuria seems to be an independent death predictor in hemoglobin S cases. SCD cases exhibit hyperfiltration and albuminuria as early as infancy, indicating severe early glomerular dysfunction [6]. The current therapy strategy for albuminuria is comparable to that of other proteinuric renal disorders, with angiotensin converting enzyme (ACE) inhibitors and, more recently, angiotensin receptor blockers serving as the mainstays. There are no documented trials of long-term proteinuria treatments for SCD. However, short-term therapy with ACE inhibitors reduces microalbuminuria and macroalbuminuria considerably [7]. In addition to a reduction in glomerular hyperfiltration and hypertrophy, the administration of hydroxyurea to children led to a decline in glomerular hyperfiltration. In a recent prospective, open-label research, albuminuria improved after six months of therapy with hydroxyurea [8].

Nephrin is a transmembrane glycoprotein that acts a vital function in the formation of the filtration diaphragm and serves as the physical barrier of last resort for plasma proteins. Nephrin shedding is utilized as a marker of glomerular-specific renal injury in several contexts and was identified prior to the onset

of albuminuria in proteinuric renal illness. As Serum nephrin forms before albuminuria, it might be a good biomarker for detecting glomerulopathy in SCD at an arly stage [9]. So, the aim of the study was to investigate whether serum nephrin is a good marker of nephropathy in sickle cell anemia and compare serum nephrin versus microalbuminuria as biomarkers for sickle cell nephropathy.

MATERIALS AND METHODS

This case–control study was conducted on sixty patients diagnosed with sickle cell anemia 46 (76.7%) diagnosed with HbSS on hydroxyurea and 14 (23.3%) case are sickle thalassemia from Pediatric Hematology Unit, Faculty of Medicine, Menoufia University from December 2020 to May 2022, from all sixty sickle patients we diagnosed 10 of them as sickle nephropathy. The sickle nephropathy patients had been selected regarding to these laboratory findings and criteria: high serum level of urea and creatinine, epidermal growth factor receptor ≤ 90 mL/min/1.73 m^2, nocturnal hypertension, microalbuminuria: ≥ 30 mg/L, and frequent vaso-occlusive crises [10, 11]. In addition, 60 apparently healthy children were considered as a control group matched to the patient group in age and sex. Informed consent was obtained from the guardian of each patient or control before participation included full explanation of the study.

Ethical approval, Scientific and Ethical Committee, Menoufia University, Faculty of Medicine approved the study protocol with approval number 11/2020 PEDI 29.

Sample size determination, a previous study [12] reported that NCR (Nephrin creatinin ratio) was significantly associated with albuminuria (odds ratio estimate = 1.002, 95% confidence interval (CI): 1.001, 1.003, p = 0.0003). The sample was calculated at power 80% and confidence level 95%, so the required sample was sixty cases.

Study outcomes, the primary outcome measures if serum nephrin was considered a good biomarker in identifying sickle nephropathy and comparing it with urinary microalbumin in sickle nephropathy patients. The secondary outcome was to determine correlations of both biomarkers with severity of SCD by variable laboratory investigations to patients.

Study methods, all participants were subjected to full history, general examination, anthropometric measurements, and vital signs including nocturnal blood pressure. Detailed systemic examination included central nervous system, cardiovascular system, chest, abdominal examination as splenomegaly and hepatomegaly.

Laboratory investigations included complete blood picture on Sysmex XN-10 Analyzer (Sysmex, Japan), hemoglobin electrophoresis was done on MiniLITE electrophoresis automated analyzer (CELL Diagnostic, Germany), serum ferritin, kidney function tests and liver function tests were done on AU680 automated analyzer (Beckman Coulter, USA), and estimation of glomerular filtration rate (GFR) was calculated by using Schwartz formula for children. Estimation of microalbumin in urine using immunoturbidimetric assay using kit provided by (HEALES, China). Serum nephrin was estimated by enzyme linked immunosorbent assay (ELISA) using kit provided by (SUNRED, China), according to manufacturer instructions.

Data were collected, tabulated, statistically analyzed using an IBM personal computer with Statistical Package of Social Science (SPSS) version 20 (SPSS, Inc, Chicago, Illinois, USA). Quantitative data were presented in the form of mean, standard deviation (SD), range, and qualitative data were presented in the form numbers and percentages. Chi-square test (χ^2) was used to study association between two qualitative variables. Mann–Whitney test (nonparametric test) was used for comparison between two groups not normally distributed having quantitative variables. Spearman's correlation was used to correlate between quantitative variables. ROC curve is a graphic representation of the relationship between sensitivity and specificity at different cut-off points for a diagnostic test. Significance level was set at p-value < 0.05.

RESULTS

In the current study, there was no statistically significant difference between cases and controls regarding age and sex. Consanguinity was significantly elevated in cases group. Weight, height, and body mass index (BMI) were significantly decreased in cases than controls. Regarding treatment, all patients received folic acid, 95% of them received L-carnitine, 76.7% of them were on hydroxyurea, and 51.7% of them were on piracetam (*table 1*). Hemoglobin, hematocrit (HCT), mean corpuscular volume (MCV), mean concentration hemoglobin (MCH) were significantly lower in cases than controls. Serum Ferritin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), urea and creatinine were significantly higher in cases than controls. Hemoglobin A1 was significantly lower in cases than in controls. Hemoglobin A2 was significantly higher in cases than in controls (*table 2*). Serum nephrin and urinary microalbumin were significantly higher in cases than controls, while only serum nephrin was significantly higher in sickle patients with nephropathy than without nephropathy (*table 3*). Age

and sex did not show significant difference regarding sickle patients with nephropathy or without nephropathy, while all cases with nephropathy had positive consanguinity, family history, nocturnal hypertension and significantly earlier onset of diagnosis than cases without nephropathy, liver and kidney function were significantly higher in cases with nephropathy than cases without nephropathy, while GFR was significantly lower in cases with nephropathy than cases without nephropathy (*table 4*). There was a significant positive correlation between serum nephrin and serum ferritin, urea, creatinine and hemoglobin F. There was a significant positive correlation between microalbuminuria and creatinine level (*table 5*).

The ROC curve revealed that at a cutoff point more than 13 ng/dL serum nephrin had sensitivity (100%), specificity (92%) to detect nephropathy among SCD patient, while at cutoff point more than 29.5 mg/dL microalbuminuria had sensitivity (60%), specificity (82%) to detect nephropathy among SCD patients (*table 6, figure*).

Table 1
Comparison between studied groups regarding their demographic data, anthropometric measurements and clinical data

Studied variables	Cases (*n* = 60)	Controls (*n* = 60)	Test of significance	*p*-value
Age, years: median range	9.00 2.00–18.0	9.50 4.00–18.0	U 0.540	0.589
Gender, *n* (%): male female	31 (51.7) 29 (48.3)	32 (53.3) 28 (46.7)	χ^2 0.022	0.881
Consanguinity, *n* (%): yes no	40 (66.7) 20 (33.3)	10 (16.7) 50 (83.3)	χ^2 20.0	**0.001***
Weight, kg: median range	25.0 9.00–55.0	34.5 19.5–75.0	U 3.14	**0.002***
Height, m: mean ± SD	1.23 ± 0.23	1.37 ± 0.21	t-test 2.55	**0.011***
BMI, kg/m^2: median range	17.1 12.2–24.0	18.1 15.3–25.8	U 2.77	**0.005***
Family history of hemolytic disorders, *n* (%): positive negative	42 (70) 18 (30)	–	–	–
Type of crisis, *n* (%): painful hemolytic no	34 (56.7) 20 (33.3) 6 (10)	–	–	–
Pallor, *n* (%): yes no	39 (65) 21 (35)	–	–	–
Onset of diagnosis, months: mean ± SD median range	7.62 ± 3.02 7.50 3–15	–	–	–
Surgical history, *n* (%): tonsillectomy appendectomy splenectomy no	4 (6.70) 2 (3.30) 10 (16.66) 44 (73.34)	–	–	–
Splenomegaly, *n* (%): yes no	10 (16.7) 50 (83.3)	–	–	–
Splenectomy, *n* (%): yes no	10 (16.66) 50 (83.34)	–	–	–
Nocturnal hypertension, *n* (%): yes no	10 (16.7) 50 (83.3)	–	–	–
Hydroxyurea, *n* (%): yes no	46 (76.7) 14 (23.3)	–	–	–
Folic Acid, *n* (%): yes no	60 (100) 0 (0.00)	–	–	–
L-Carnitine, *n* (%): yes no	57 (95.0) 3 (5.00)	–	–	–
Piracetam, *n* (%): yes no	31 (51.7) 29 (48.3)	–	–	–

*Note. U – Mann–Whitney test; significance level at p-value < 0.05; * – significant.*

Table 2
Laboratory investigations of the studied groups

Studied variables	Cases (*n* = 60)	Controls (*n* = 60)	Test of significance	*p*-value
Hemoglobin, gm/dL: mean ± SD	8.85 ± 1.42	12.5 ± 0.99	t-test 12.8	**< 0.001****
HCT, %: median range	25.9 14.5–34.7	38.5 22.9–45.1	U 7.01	**< 0.001****
MCV, fL: median range	76.1 60.0–91.0	87.4 71.7–94.8	U 5.83	**< 0.001****
MCH, pg: median range	25.8 20.0–39.5	28.4 20.8–32.0	U 3.74	**< 0.001****
WBCs, × 10^3/mm^3: median range	8.85 3.80–26.1	8.95 5.10–10.5	U 0.056	0.956
Platelets, × 10^3/mm^3: median range	285.0 151.0–1200	226.0 153.0–434.0	U 0.535	0.593
Ferritin, ng/mL: median range	702.5 13.0–3860	109.0 24.0–140	U 5.15	**0.001****
AST, IU/L: median range	35.0 18.0–117.0	25.5 13.0–34.0	U 5.63	**< 0.001****
ALT, IU/L: median range	21.0 7.00–85.0	18.1 12.0–29.0	U 2.76	**0.006***
Urea, mg/dL: mean ± SD	26.9 ± 7.25	9.93 ± 2.58	t-test 16.2	**< 0.001****
Creatinine, mg/dL: median range	0.60 0.40–1.00	0.40 0.20–0.50	U 6.63	**< 0.001****
Hemoglobin A1: median range	25.2 0.00–70.0	97.2 97.0–98.0	U 7.70	**0.001****
Hemoglobin F: mean ± SD median range	13.6 ± 12.8 9.95 0.00–43.7	–	–	–
Hemoglobin S: mean ± SD median range	82.4 ± 7.54 59.5 28.2–533	–	–	–
Hemoglobin A2: mean ± SD median range	3.21 ± 1.22 3.00 1.30–7.00	2.63 ± 0.35 2.75 2.00–3.00	U 2.68	**0.007***

*Note. U – Mann–Whitney test; * – significant; ** – highly significant.*

Table 3
Comparison between serum nephrin and urinary microalbuminuria among the studied groups

Studied variables	Cases (*n* = 60)	Controls (*n* = 60)	Test of significance	*p*-value
Serum nephrin, ng/mL: median range	6.00 3.00–30.0	0.40 0.01–1.00	U 7.77	**0.001***
Microalbuminuria, mg/dL: mean ± SD	24.8 ± 7.18	9.05 ± 2.57	t-test 15.1	**0.001***
Studied variables	**SCD with nephropathy (*n* = 10)**	**SCD without nephropathy (*n* = 50)**	**Test of significance**	***p*-value**
Serum nephrin, ng/mL: median range	15.5 14.0–30.0	5.00 3.00–14.0	U 5.50	**0.001***
Microalbuminuria, mg/dL: mean ± SD	28.5 ± 9.27	24.1 ± 6.55	t-test 1.80	0.077

*Note. * – significant; U – Mann–Whitney test.*

Table 4
Comparison between cases with nephropathy and without nephropathy regarding their demographic, clinical data and laboratory investigations

Studied variables	SCD with nephropathy (*n* = 10)	SCD without nephropathy (*n* = 50)	Test of significance	*p*-value
Age, years: mean ± SD	11.6 ± 5.13	8.97 ± 4.49	t-test 1.68	0.098
Gender, *n* (%): male female	3 (30.0) 7 (70.0)	28 (56.0) 22 (44.0)	χ^2 2.25	0.133
Consanguinity, *n* (%): yes no	10 (100) 0 (0.00)	30 (60.0) 20 (40.0)	χ^2 6.00	**0.023***
Family history, *n* (%): positive negative	10 (100) 0 (0.00)	32 (64.0) 18 (36.0)	FE 5.14	**0.025***
Onset of diagnosis, months: mean ± SD median range	4.40 ± 1.17 4.50 3.00–6.00	8.30 ± 2.93 8.00 3.00–15.0	4.00	**0.001***
Nocturnal hypertension, *n* (%): yes no	10 (100) 0 (0.00)	0 (0.00) 50 (100)	FE 60.0	**0.001***
AST, IU/L: median range	47.0 39.0–117.0	34.5 18.0–71.0	U 4.11	**0.001***
ALT, IU/L: median range	42.5 33.0–85.0	20.0 7.00–105.0	U 4.31	**0.001***
Urea, mg/dL: median range	38.5 31.0–44.0	26.0 12.0–39.0	U 4.79	**0.001***
Creatinine, mg/dL: median range	0.90 0.68–1.00	0.60 40.0–90.0	U 4.06	**0.001***
Uric acid, mg/dL: median range	7.10 4.80–8.10	5.50 4.50–8.90	U 1.61	0.106
Epidermal growth factor receptor, mL/min: median range	91.0 50.0–133.0	117.5 65.0–217.0	U 2.61	**0.009***

*Note. Significance level at p-value < 0.05; * – significant; U – Mann–Whitney test; FE – Fisher exact test.*

Table 5
Correlation between serum nephrin and microalbuminuria with laboratory investigations among the studied cases (*n* = 60)

Studied variables	Serum nephrin		Microalbuminuria	
	r	*p*-value	r	*p*-value
Hemoglobin	–0.209	0.109	0.040	0.760
HCT	–0.235	0.071	0.068	0.606
MCV	0.108	0.413	–0.174	0.184
MCH	–0.031	0.813	–0.134	0.309
WBCs	0.180	0.169	0.038	0.775
Platelets	0.044	0.736	0.099	0.450
Ferritin	0.256	**0.048***	0.028	0.834
SGOT	–0.016	0.904	–0.084	0.524
SGPT	0.145	0.268	–0.186	0.155
Urea	0.346	**0.007***	0.154	0.239
Creatinine	0.476	**0.001***	0.289	**0.025***
Uric acid	0.119	0.363	0.126	0.339
GFR	–0.216	0.098	0.120	0.362
Hemoglobin A1c	–0.398	**0.002***	–0.175	0.181
Hemoglobin F	0.282	**0.029***	0.129	0.327
Hemoglobin S	0.196	0.133	0.044	0.740
Hemoglobin A2	0.009	0.945	0.010	0.942
Serum nephrin	–	–	0.041	0.754

Note. r – Spearman's correlation.

DISCUSSION

SCD is an autosomal recessive hemoglobinopathy that affects more than 300,000 newborns per year worldwide. Clinical and genetic factors have been reported as influencing the development of sickle cell nephropathy [13]. In this study, there was no significant variance among cases and controls as regards age and sex, while consanguinity was significantly high in cases group. and this agreed with Youssry et al. [14] who reported that there was no significant variance among cases and controls as regards age and sex, while these results are disagreement with Moraleda et al. [15], who reported there was a significant variance among their SCD group and healthy control group as regards age and sex. Most of the previous studies supporting our results revealed a link between SCA and parental consanguinity and concluded that societies with high rates of consanguineous marriages had a much greater prevalence of hereditary blood diseases such as sickle cell anemia [16, 17].

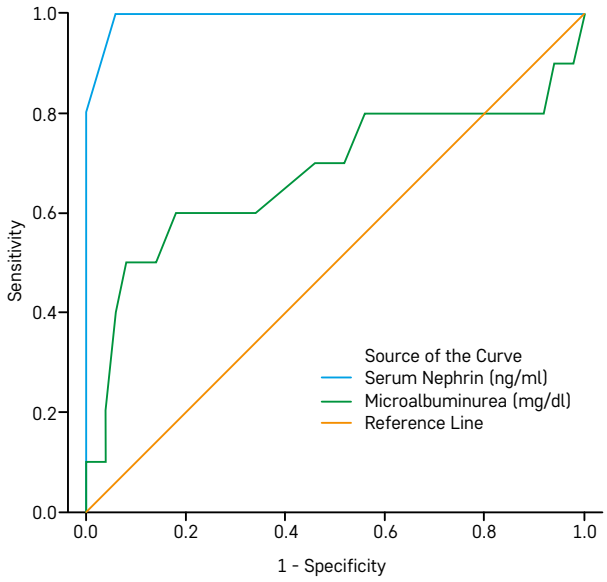
The weight, height and BMI were significantly decreased in cases than in controls. This was in line with other studies who revealed compared to children with a normal hemoglobin genotype, children with sickle cell anemia have a lower BMI and anthropometric characteristics. [18] Mean hemoglobin, HCT, MCV, MCH were significantly lower in cases than in controls, while the mean of ferritin, ALT, AST, urea, and creatinine were significantly elevated in cases than in controls. Additionally, hemoglobin A1 was significantly declined

Table 6
Sensitivity and specificity of serum nephrin and microalbuminuria in detection of cases of sickle cell nephropathy

Studied variables	AUC	*p*-value	Cut-off point, mg/dL	Sensitivity, %	Specificity, %	PPV, %	NPV, %	Accuracy, %
Serum nephrin	0.994	**0.001***	≥ 13	100	92	71	100	93
Microalbuminuria	0.677	0.079	≥ 29.5	60	82	40	91	78

Note. AUC – area under the curve; PPV – positive predictive value; NPV – negative predictive value.

Figure
ROC curve analysis of serum nephrin and urinary microalbumin for the detection of sickle cell nephropathy



in cases than in controls. hemoglobin A2 was significantly higher in cases than controls. Hemoglobin F and hemoglobin S were founded in cases only. Our study agrees with [19] and [20] as both reported that low hemoglobin and HCT concentration in cases with SCD than in controls, on the other hand our results disagree with [19] who reported that mean MCV that was higher among HbSS subjects than in controls, this variability in results can be explained by difference in ethnic group and sample size. Also, these results agreed with another study which reported that hemoglobin A1 was lower in SCD patients but hemoglobin F, hemoglobin S, hemoglobin A2 were significantly elevated in sickle cell anemia cases than in controls [19].

In our study there was no significant difference between sickle cell anemia cases with nephropathy or without nephropathy regarding their age and sex. All cases with nephropathy had positive consanguinity and family history, their mean age of onset of diagnosis was significantly earlier, and all of them had nocturnal hypertension. Our findings are in line with Isaza-López et al. [21] who revealed there was no significant variance among SCD cases with nephropathy and in controls regarding to sex. In contrast to our results, Geard et al. [22] and Nding'uri [23] reported that age, sex were significant risk factors related with renal dysfunction development in SCD cases. Also, Benneh-Akwasi et al. [24] demonstrated nocturnal hypertension is a significant risk factor in SCD patients.

Both serum nephrin and microalbuminuria were significantly elevated in cases than in controls, while only serum nephrin was significantly elevated in sickle cases with nephropathy than with no nephropathy. These findings are in line with Kadhim & AlDujaili [25], who demonstrated there was significant elevation in serum level of nephrin in sickle cell anemia cases than in controls, Also, other studies [26] and [27] who reported the involvement of nephrin in proximal tubule dysfunction in diabetic nephropathy, all investigations had clarified the function of nephrin in podocytes injury. Similarly, other studies [28] and [29] revealed that nephrin, also known as vascular endothelial growth factor, is a proangiogenic factor that is elevated in normoalbuminuria, a fact that may be utilized as indicators for early identification of nephropathy and glomerulopathy. On the other hand, this research disagrees with other one who found microalbuminuria is a significant risk factor in sickle cell nephropathy [24]. At a cutoff point more than 13 ng/mL serum nephrin had higher sensitivity about 100% and specificity about 92% to detect nephropathy, while at a cutoff more than 29.5 mg/L microalbuminuria had sensitivity around 60% and specificity about 82% to detect nephropathy. Serum nephrin had higher sensitivity and specificity than microalbumin as biomarker in sickle nephropathy. The limitation of this study was that serum nephrin and urinary microalbumin could not be measured serially over the course of disease.

CONCLUSION

Serum nephrin could be considered a good diagnostic biomarker for the early detection of the sickle cell nephropathy than urinary microalbuminuria.

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CONFLICT OF INTEREST
The authors declare that there is no conflict of interest.

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