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Sickle Hemoglobin-Related Nephropathy: an Overview on Pathophysiology, Diagnosis, and Treatment

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Abstract
Sickle cell disease (SCD) is a common hemoglobinopathy in the world with progressive multi organ failure. Many organs have been affected in this disease, but sickle cell nephropathy (SCN) is a major complication which affects the quality of life in these patients. SCN has a wide range of renal manifestations such as asymptomatic microalbuminuria, hyposthenuria, hematuria, frank proteinuria, nephrotic syndrome and end stage renal disease (ESRD). Nowadays novel biomarkers such as N-acetyl-beta-D-glucosaminidase (NAG), kidney injury molecule-1 (KIM-1) and transforming growth factor β (TGF-β) has allowed the early detection of the kidney involvement in sickle cell disease. The angiotensin converting enzyme (ACE) inhibitor drugs such as captopril or enalapril and also ACE receptor blockers (losartan) have beneficial effects in albuminuria or proteinuria. Also endothelin-1 (ET-1) receptor antagonists have a promising role in glomerular injury in SCD. In sickle patients who develop ESRD, renal replacement therapy can be life- saving. In recent years, kidney transplantation is the only curative treatment for advanced chronic kidney disease in these patients.

Keywords: Sickle cell; Nephropathy; Kidney.

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Introduction
Sickle cell disease (SCD) is one of the most common hereditary hemoglobinopathy in the world. Sickle cell mutation results from the substitution of glutamic acid to valine at the sixth position of the beta chain leading to formation of hemoglobin S (Hb S). In SCD, the predominant hemoglobin (often more than 50 percent) is Hb S. In subjects, who have one sickle mutant beta gene and one normal beta gene; have sickle cell trait (AS). Sickle cell syndromes are various genotypes where one of the beta-globin gene mutations is a sickle cell mutation and includes Hb SS, Hb $S\beta^0$, Hb SC and Hb $S\beta^+$. The severity of disease in Hb SS and Hb $S\beta^0$ is much more than in Hb SC and Hb $S\beta^+$. In hypoxic condition, Hb S deoxygenated and then polymerized. This polymerization leads to deformation of erythrocytes to sickle cells.

The quantity of Hb S polymerization is the most important factor in disease severity.
The survival of rigid sickle cells has been decreased. These RBCs do not have flexibility to cross microcapillaries leading to extravascular and intravascular hemolysis and vasoconstriction with tissue ischemia injury (1). The majority of Iranian patients with SCD are living in southern parts of our country especially Khuzestan province (2). Unlike thalassemia, which has a preventive program in Iran from 1995, there is no specific program for prevention of SCD in Iran (3). In recent years, due to advances in diagnosis and medical management of patients with SCD, the survival of them has been dramatically improved. Therefore, a variety of chronic morbidities have emerged in these patients in recent years (4).

Kidney is one of the vital organs that could be affected in SCD. In patients with sickle cell disease, microalbuminuria is the first manifestation of sickle cell nephropathy. The incidence of this complication increases with aging. Other renal complications of SCD include impaired ability to concentrate urine, hematuria, papillary hypertrophy and necrosis, predisposition to urinary tract infections and renal medullary carcinoma (5). In this review, the renal manifestations of sickle cell disease, with focus on mechanisms of nephropathy have been discussed.

Pathophysiology

The mechanism of nephropathy in SCD is related to both vaso-occlusive phenomenon and also hemolysis related vasculopathy (6). Haymann et al. in a study have been shown that the pathophysiology of hyperfiltration in patients with sickle cell disease has been related to hemolysis associated vasculopathy (7). Inner medulla of kidney has some specific properties such as acidosis, low blood flow, low oxygen tension and hyperosmolarity which may be related to renal injury in SCD. Therefore, this part of kidney is an appropriate site for polymerization of Hb S and sickling of erythrocytes. This phenomenon results in occlusion of microvascular system and subsequent ischemia in the renal papillae (8). Intravascular hemolysis results in a depletion of nitric oxide (NO) and decreased NO bioavailability may lead to endothelial dysfunction (9).

Endothelin-1 (ET-1) is an endothelium derived peptide which is a potent vasoconstrictor with proliferative and proinflammatory properties. This peptide is released in response to hypoxia, shear stress, inflammatory cytokines and angiotensin II, which these parameters are common in SCD. Moreover, the level of ET-1 is increased in urine and plasma of patients with sickle cell disease (10). Also, ET-1 can increase the reactive oxygen species (ROS). ROS acts as a defense mechanism against bacterial infections. However, when the production rate of ROS is more than endogenous antioxidants, pathological cellular damage occurs in response to oxidative stress (11, 12). In SCD patients, neutrophils, platelets and erythrocytes produce higher level of ROS in comparison to healthy control (13, 14). The increased oxidative stress and also increased ROS have a critical role in the pathogenesis of chronic kidney disease in SCD (5). Becker et al. have demonstrated that following an ischemic damage, the release of prostaglandins increases which may result in increased e-GFR and glomerular injury and finally glomerulosclerosis (16). Chronic hemolysis result in iron accumulation in the kidney, leading to proliferation of mesangial cells and interstitial with glomerular fibrosis (17, 18). One of the most reliable methods for assessment of iron deposition in different vital organs such as kidneys is magnetic resonance imaging (MRI). Quantitation of kidney iron stores could be done by means of MRI T2* or R2 in thalassemia and sickle cell disease (19-22). In a study by Schein and their colleagues, MRI was performed in 75 SCD, 73 thalassemia major (TM) and 16 healthy control in order to assess kidney iron stores. This author has found that kidney R2 has a strong correlation with level of serum lactate dehydrogenase. Also kidney R2 decreases with advancing age. Moreover, Schein et al. have found there is no correlation between kidney R2 with hepatic iron concentration and cardiac R2. These authors have concluded that intravascular hemolysis, not chronic transfusion leads to kidney hemosiderosis (22).

Manifestation of sickle cell nephropathy

Hematuria is one of the most common manifestation of sickle cell nephropathy. The prevalence of hematuria in SCD ranges between 13% and 30% (6). In these patients, sometimes hematuria is microscopic and painless, occasionally macroscopic and painful. Hematuria in SCD is often self-limited but can be severe enough to require transfusion. Minor bleeding in patients with sickle cell is due to small microinfarct, but renal papillary necrosis with sloughing of ischemic papilla can result in severe bleeding (23). The most probable etiology of hematuria is due to vaso-occlusive crisis, microinfarction and then subsequent ischemic parenchymal damage. Involvement of left kidney is more than right kidney (24). Another factors that increase the risk of papillary necrosis include systemic vasculitis, pyelonephritis, diabetes mellitus, analgesic use, cirrhosis, urinary tract obstruction and renal vein thrombosis (25). Hemoglobinuria may be due to glomerular damage or chronic kidney disease (CKD). The incidence of hemoglobinuria is approximately 15-42% of patients with sickle cell disease (26, 27). One of the morbidities in SCD patients in the second to fourth decade of life is renal medullary carcinoma which

can be associated with macroscopic hematuria. Renal medullary carcinoma has a poor prognosis (6).

Glomerulopathy

In SCD patient's glomerular lesions and azotemia have been associated with poor prognosis. Also increased GFR and glomerular capillary hypertension may result in glomerular function abnormalities (6). Glomerular size increases with advancing age and glomerular congestion starts from early childhood (28). Three mechanisms are responsible for hyperfiltration in patients with SCD. At first, sickling of RBC leads to ischemia in medulla and consequently secretion of prostaglandin and nitric oxide (No). These elements lead to increase in blood flow. The second mechanism is due to anemia. Severe anemia causes increase in cardiac output and decrease in renal vascular resistance and finally GFR increases. The third mechanism is due to hemolysis in SCD. In process of hemolysis, the level of heme and heme oxygonase-1 increases. The increased rate of heme disintegration result in overproduction of carbon monoxide (CO), which is a strong vasodilator (6). Proteinuria and hyperfiltration are the most prevalent manifestations of glumerulopathies in SCD. Microalbuminuria in SCD patients can be detected from late childhood. The incidence of this complication increases with advancing age. Microalbuminuria defined as a urinary albumin to creatinine ratio of more than 4.5 mg/mmol. Microalbuminuria can develop into frank proteinuria (protein to creatinine ratio more than 50mg/mmol) and finally nephrotic syndrome (>3gr total protein / 24h).

The prognosis of nephrotic syndrome in these patients is very poor (23). Albuminuria is more common in patients with homozygous Hb S (SS) than heterozygous AS and is rare in patients with genotype SC (6). Hyperfiltration which means e-GFR > 150 mL/min/1.73 m^2, could be detected in 14-76% in SCD, but in the majority of cases, the GFR decreases in the second decade of life (29, 30). Also the most prevalent histopathological picture in the kidney of sickle cell patients is focal and segmental glomerulosclerosis which may lead to membranoproliferative glomerulonephritis. Sometimes in these patients thrombotic microangiopathy, immune complex glomerulopathy and even amyloidosis may occur (31, 32).

Tubular abnormalities

One of the most common tubular function abnormalities in sickle cell is hyposthenuria that even may occur in patients with sickle cell trait (AS). In children hyposthenuria often results in enuresis. In childhood until the age of 10 years, hyposthenuria is reversible but with advancing age, this morbidity became irreversible. The etiology of this phenomenon is due to a permanent injury to microvasculature in association with pathological distention of outer medullary capillaries and blind-ending inner medullary vasa recta (23). Patients with SCD can present both proximal and distal tubular dysfunction (6). Other presentations of glomerular disease in sickle cell include hyperchloremic metabolic acidosis, hyperkalemia, hyperphosphatemia, increased secretion of uric acid and increased creatinine clearance. In 10% of sickle cell patients, acute kidney injury can occur due to volume depletion, renal vein thrombosis, papillary necrosis, rhabdomyolysis and urinary tract obstruction secondary to blood clots (5).

Chronic kidney disease (CKD) and end stage renal disease (ESRD)

The different renal complications of SCD such as glomerular dysfunction, tubulopathy and hematuria can lead to end stage renal disease (6). In a large cohort study on sickle cell patients, renal failure has been detected in 12% of patients with a median age of 37 years. Moreover, advanced CKD is the most common cause of death in SCD (33). Baddam et al. have reported that low hemoglobin concentration and use of NSAID are two predisposing factors for CKD (34). McClellan et al. in a large retrospective study on 442017 patients with ESRD and SCD between 2005 and 2009 have reported that 0.1% of patients who are receiving hemodialysis have ESRD in the background of sickle cell disease. These authors have shown that mortality rate between patients with SCD-ESRD receiving hemodialysis is 2.8 times higher than non-sickle cell patients (35).

Novel biomarkers in diagnosis of sickle cell nephropathy

Early detection of sickle cell nephropathy by routine laboratory tests such as BUN and creatinine is not

possible. Therefore, novel biomarkers are necessary in order to predict sickle cell nephropathy in early stages (36).

NAG

N-acetyl β-D-glucosaminidase (NAG) is a lysosomal enzyme that has been found in the renal proximal tubules. The level of this marker in urine increases in early stages of idiopathic membranous nephropathy, focal segmental glomerulosclerosis, glomerular hypertrophy and minimal chain disease (37). Normal NAG activity in the urine is less than 2U/L (38). Sundaram et al. in a study on 116 patients with sickle cell disease have shown that there is a strong association between NAG and albuminuria (39). In another study which was performed on 38 patients with sickle cell (19 with albuminuria and 19 without albuminuria) authors have demonstrated that there is a potent correlation between NAG activity and albuminuria. Also urine hemosiderin has been correlated with the presence of albuminuria (40).

KIM-1

Kidney injury molecule-1 (KIM-1) is another biomarker for detection of tubular injury. This marker is undetectable in healthy subjects, but after tubular injury, the level of KIM-1 increases in urine. Moreover, in CKD, the elevation of KIM-1 has been shown (41). After kidney injury, KIM-1 can be found in all three segments of the renal tubules, but the maximum concentration of this biomarker can be found in apical membrane of the proximal tubule. Also soluble KIM-1 can be found in the urine of patients with acute tubular necrosis (ATN), therefore KIM-1 is a promising biomarker of damage to the proximal tubule (42, 43). KIM-1 has a strong association with albuminuria in patients with sickle cell disease (39). Hamideh et al. in another study have been shown that KIM-1 has a correlation with albuminuria in SCD (40).

NGAL

Neutrophil gelatinase associated lipocalin (NGAL) is another biomarker that produces in ascending loop of henleh and collecting duct cells. In kidney injury NGAL secretion from the epithelial cells of kidney occurs. After acute kidney injury, the reabsorption of NGAL in tubular cells decreases and consequently the level of urinary NAG increase (44). Mitsnefes et al. have shown that there is a strong correlation between serum NGAL and measured GFR. These authors have concluded that NGAL is an appropriate marker for monitoring and grading of CKD (45). Also urinary NGAL is a useful marker for production of acute kidney injury (46, 47). Mohtat et al. have found that there is no difference about urinary NAGL level between sickle cell patients and healthy control. These authors have concluded this finding may be due to exclusion of unstable patients with frequent vaso-occlusive crisis from study population (48). Sundaram et al. in another study have shown no relationship between urinary NGAL and albuminuria. Indeed, patients with SCD have subnormal NGAL concentration in the urine (39). These finding may be due to 2 mechanisms. At first proximal tubules are over functional in SCD, thus reabsorption of NGAL by proximal tubules increases. Secondly the damage to distal tubules in sickle cell patients may result in prevention of NGAL secretion by distal tubules. Laurentino et al. have concluded that the principal role of NGAL in SCD may be excluding of other mechanisms of renal injury which are associated with increased urinary NGAL (36).

L-FABP

Liver type fatty acid binding protein (L-FABP) is a useful biomarker for detection of acute kidney injury (AKI) in early stages. The expression of L-FABP gene in renal ischemia and also tubulo-interestitial damage increases. Also this marker can be used as a predictor for early and late-stages of chronic kidney disease (49, 50). It seems that L-FABP has no correlation with albuminuria in SCD (39).

MCP-1

Monocyte chemotactic protein-1 (MCP-1) is another marker of mononuclear cell inflammation in ischemia induced acute kidney injury (42). Santos et al. have shown that patients with sickle cell disease have higher levels of MCP-1 than healthy control and after treatment with hydroxyurea, the concentration of MCP-1 returns to normal (51).

TGFβ-1

Transforming growth factor β-1 (TGFβ-1) is a strong fibrogenic growth factor that could play an important role in the pathogenesis of sickle cell nephropathy (52). TGF β-1 has a critical role in

renal fibrogenesis and nephron loss due to different mechanisms such as apoptosis of endothelial cells and podocytes. Also this biomarker causes epithelial to mesenchymal cell transition (53). Moreover, renin-angiotensin aldosterone system (RAAS) can activate TGFβ-1 pathway. The intra-renal RAAS system may have a critical role in the pathogenesis of sickle cell nephropathy (52). Mohtat et al. have shown that patient with SCD have a higher urinary TGFβ-1 concentration in comparison with normal healthy control. Also they have concluded that the level of this biomarker in sickle cell patients with anemia (Hb < 9 gr/dL) was much higher than patients without anemia. Also urinary TGFβ-1 was lower in Hb SS patients on hydroxyurea (HU) in comparison with Hb SS patients who were not on HU (48). This urinary marker has a positive correlation with microalbuminuria and e-GFR in sickle cell disease (54).

RBP

Retinol binding protein (RBP) acts as a biomarker for diagnosis of proximal tubular dysfunction. Also urinary RBP is correlated to progression of CKD (55). Unal et al. have done a study on 45 pediatric and 10 adult patients with SCD and 20 healthy children and 10 healthy adults as control group. In this study there was no difference in urinary RBP level between patients with SCD and healthy control group (56). In another study in Saudi Arabia, the urinary RBP level has been evaluated in children with SCD (Hb SS) and patients with sickle cell trait (Hb AS). The urinary excretion of RBP was significantly higher in homozygous Hb SS than heterozygote group (Hb AS) (57).

Cystatin C

Cystatin C is a cysteine protease inhibitor and an ideal marker for detection of impaired kidney function. This marker in contrast to creatinine, has no correlation with age, gender, race or muscle mass. Also cystatin C is superior to creatinine for diagnosis of glomerular dysfunction (58, 59). Cystatin C is a useful marker for estimation of GFR in sickle cell disease (39). El-Gamasy et al. have performed a study in Egypt on 70 children with SCD and 40 healthy children as control group. In this study they have found that SCD patients have higher level of cystatin C in comparison to healthy control group. Also serum cystatin C was positively correlated with serum creatinine, serum ferritin, blood urea, urinary albumin to creatinine ratio, duration of iron chelator drugs consumption, and frequency of blood transfusions / year. In addition serum cystatin C was negatively correlated with hemoglobin concentration (60).

β2-Microglobulin

β2-microglobulin (β2M) is another urinary marker for evaluation of proximal tubular function disorders (61). Patients with SCD had higher urinary β2M in comparison to normal population. This marker has sensitivity and specificity for detection of tubular dysfunction in early stages of sickle cell nephropathy (56, 57, 60)

Nephrin

Nephrin is a critical marker for glomerular function and the urinary level of nephrin increases in glomerular disorders. In SCD the urinary level of nephrin increases before albuminuria (62).

Endothelin-1

Endothelin-1 (ET-1), an endothelium derived peptide, is a potent vasoconstrictor. This peptide is released in response to inflammatory cytokines, thrombin activation, hypoxia, shear stress, hemin, angiotensin II and thrombin activation (62). Patients with SCD have higher level of ET-1 in plasma. Also there is a strong correlation between urinary ET-1 and microalbuminuria (63). Ataga in a recent study has shown the association of microalbuminuria with endothelial dysfunction in patients with SCD. Also sickle cell patients have higher level of ET-1 in circulation (64).

Treatment

The two main goals of management include: 1-management of sickle cell disease, 2-management of sickle cell nephropathy (6).

Therapies for SCD

Transfusion

Regular or intermittent transfusion is one of the most important therapies in sickle cell disease which could prevent many complications of this disease such as stroke or pulmonary hypertension. The effects of chronic transfusion in prevention of sickle cell nephropathy are not clear (23). Alvarez et al. have reported that chronic transfusions before the age of 9 years have a protective role against sickle nephropathy (65). In another study, Becton

and colleagues have shown that the incidence of microalbuminuria does not differ between patients who are receiving chronic transfusion and those without transfusion (66).

Hydroxyurea

Hydroxyurea (HU) is the only pharmacologic agent which has documented benefits in treatment of SCD. It is the only FDA approved drug for the management of sickle cell disease. HU is a strong ribonucleotide reductase inhibitor that increases Hb F production and decreases the synthesis of Hb S. This drug has a critical role in preventing progression of sickle cell nephropathy to ESRD (6). HU can decrease pain, acute chest syndrome and need for transfusion. Also long term usage of HU leads to a better growth and development (23). Also in some studies have been reported that HU has documented benefits in treatment of sickle cell nephropathy (67, 68). Wang et al. in a randomized placebo controlled trial (BABY HUG) have shown that usage of HU has not any significant effect on GFR (69). Also HU could not decrease hyperfiltration in sickle cell patients (6). Aygun et al. in HUSTLE study (Hydroyurea Study of Long-term Effects) have demonstrated that hydroxyurea in SCD can decrease hyperfiltration in them. Also similar to BABY HUG study, no significant change in GFR among young children was observed in HUSTLE (70).

Hematopoietic stem cell transplantation

The only curative treatment for SCD is hematopoietic stem cell transplantation (HSCT), but has been used less frequently in adults compared to children. Newer methods of transplantation such as non-myeloablative and reduced intensity conditioning HSCT regimens have shown greater tolerability and better outcome in adults with sickle cell disease (71).

Other therapeis

Nicotinamide adenosine dinucleotide (NAD) is a redox cofactor in erythrocytes that is deficient in sickle cell disease. In a multicenter phase 3 trial, Niihara et al. have demonstrated that L-glutamine can decrease the number of vaso-occlusive crisis in patients with SCD (72). Nowadays newer drugs targeting P-selectin (crizanlizumab) or inhibiting Hb S polymerization (voxelotor) have been tested in adults with SCD. Crizanlizumab results in a significant decline in vaso-occlusive crisis rates and voxelotor improves hemolysis and consequently increases hemoglobin concentration in patients with SCD (73, 74).

Therapies for sickle cell nephropathy

Angiotensin converting enzyme inhibitors

The current treatment for sickle cell nephropathy in pediatric patients is the angiotensin converting enzyme (ACE) inhibitors. The most important etiology of SCN is vasoconstriction and progressive glomerular hypertension. The mechanism of ACE inhibitors is mainly related to dilatation of efferent arterioles which causes a decrease in glomerular pressure and microalbuminuria. Therefore, ACE inhibitors have been useful in sickle cell related renal dysfunction (33). The efficacy of enalapril and captopril in reduction of microalbuminuria in multiple studies have been shown. According to these results, National Heart Lung and Blood Institute (NHLBI) consensus panel has suggested ACE inhibitors in all of adult patients with SCD and albuminuria more than 30 mg/g (33). Quinn et al. in a study on 36 patients with SCD have demonstrated that oral losartan after 6 months results in a significant decline in albuminuria (75). McKie in another study on 36 patients with SCD have shown that ACE inhibitors can resolve microalbuminuria in 50% of cases, but these drugs have an important side effect, hyperkalemia, which limits the use of them (76). Although ACE inhibitors and losartan does not seem to have a documented effect in progression of CKD in sickle cell nephropathy (77). Some authors recommended both ACE inhibitors or angiotensin receptor type II blockers in sickle cell patients who have a persistent urinary protein to creatinine ratio above 100 mg/mmol. Moreover another benefit of these drugs is a decline in the number of times they have to pass urine at night, may be due to reduction in GFR (23)

Role of ambrisentan in SCN

Endotheline-1 (ET-1) has a significant role in renal injury in SCD. Therefore, ET-1 receptor antagonists may have a promising role in prevention of kidney dysfunction in SCD (78). Recently in studies on humanized SCD mice have been shown that ETA receptor antagonist, ambrisentan have a positive impact on glomerular function. Moreover, chronic treatment with ambrisentan results in a significant decline in albuminuria and proteinuria (78).

Management of advanced CKD in SCD

Despite effective therapies against proteinuria, some sickle cell patients will develop chronic renal failure. In these subgroup of sickle cell patients, renal replacement therapy (RRT) is indicated. When kidney function deteriorates, the endogenous production of erythropoietin decreases (23). In patients who develop progressive chronic renal disease, the GFR declines below 40 mL/min/1.73 m^2. In sickle cell patients, hemodialysis access is another important topic, because these patients due to repeated hospitalizations, have poor peripheral vein (6). Also in sickle cell patients, with ESRD who receive hemodialysis the mortality rate is much higher in comparison to non-SCD patients. The incidence of both short term and long term dialysis associated death is approximately 26% during 1 year follow up (35, 79). Although kidney transplantation has specific complications, but this method is still the choice of treatment in patients with SCD and ESRD. Kidney transplantation has a better prognosis compared to hemodialysis in patients with SCD (6). Moreover, the 1-year acute rejection rate and graft survival were not significantly different in comparison to patients who have received kidney transplantation due to other reasons (23). Kidney transplantation results in production of endogenous erythropoietin and responsiveness of bone marrow to erythropoietin stimulating agents (80). In recent years, the survival of sickle cell patients who have received kidney transplantation has improved dramatically and the 6 years survival is comparable to patients with diabetes and ESRD (81).

Conclusion

Renal dysfunction is one of the most important complications of sickle cell disease. Manifestations of sickle cell nephropathy have a wide range from asymptomatic albuminuria or hyposthenuria to overt advanced chronic kidney disease. Pharmacologic agents in treatment of renal dysfunction in SCD includes ACE inhibitors and ACE receptor blockers. Endothelin-1 receptor antagonists have useful effects in sickle cell nephropathy. In patients with SCD and ESRD, renal replacement therapy including hemodialysis and kidney transplantation could result in improved survival.

Conflict of Interest

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