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A Review of Prevalence, Risk Factors and Clinical Significance of Microalbuminuria in Patients with Sickle Cell Anaemia.

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Abstract

Sickle cell anaemia (SCA) is an inherited condition characterized by complications in various organs including the kidney. Sickle cell nephropathy results from damage to the nephrons, consequent upon renal haemodynamic response to recurrent episodes of sickling within the renal microvasculature. Microalbuminuria (MA) is an early indicator of such renal injury. The aim of this review was to determine the prevalence, risk factors and clinical significance of microalbuminuria in patients with sickle cell anaemia. Literature search using the search terms: Microalbuminuria, sickle cell disease, sickle cell nephropathy (SCN) of original articles, systematic reviews and review articles selected online through HINARI and other relevant websites were obtained. More recent articles were given preference. Thirty articles were selected. Other source materials were obtained from relevant websites and haematology textbooks. There was a rising trend for the prevalence of microalbuminuria with increasing age. Low haemoglobin and high glomerular filtration rates were consistently associated with microalbuminuria. Other variables including high blood pressure, total white blood cell count, markers of haemolysis and female gender were associated to a variable extent. There is strong evidence indicating that microalbuminuria is highly prevalent in patients with SCA. The natural progression of microalbuminuria has not yet been established, however, therapeutic trials with angiotensin converting enzymes inhibitors (ACE I) has shown promising results in reducing microalbuminuria.

Keywords: Prevalence, risk factors, clinical significance, microalbuminuria, Sickle cell anaemia.

Introduction

Sickle cell disease is an inherited condition characterised by a point mutation on the beta globin gene, resulting in the substitution of valine for glutamic acid at the sixth position of the beta chain of the haemoglobin (Hb) molecule. The resulting haemoglobin molecule is rendered insoluble upon deoxygenation, red cells containing such Hb molecules assume the 'classical' sickled shape and become less deformable; this shape change leads to widespread obstruction in the microcirculation, causing infarctions of various organs (Sharpe and Thein, 2014). The homozygous form of the disease (HbSS), also known as sickle cell anaemia (SCA) is associated with a severe clinical course, in contrast, the heterozygotes (HbAS/Sickle cell trait) form is an asymptomatic condition with no anaemia and normal blood film morphology. Other double heterozygotes form includes, HbSC, HbSD and HbS/beta thalassemia. These are associated with a milder disease course (Sharpe and Thein, 2014).

Epidemiology of SCA

Sickle cell disease affects people mostly from Africa, Mediterranean and the Middle East. The

prevalence of the heterozygotes form is partly responsible for this distribution. The prevalence is high in West Africa sub region because of the protection the carrier trait (HbAS) confer against malaria (Figure1), for example in Nigeria, considered to be the world largest sickle cell pool,

the prevalence of HbAS is 20 to 25% while the incidence of the homozygous form (HbSS) is 2-3% (Abdu et al.,2011). In the USA, the prevalence of the heterozygous form (HbAS) is 8%, and the homozygous form occurs in 1 in every 400 births (Guasch et al., 2006).

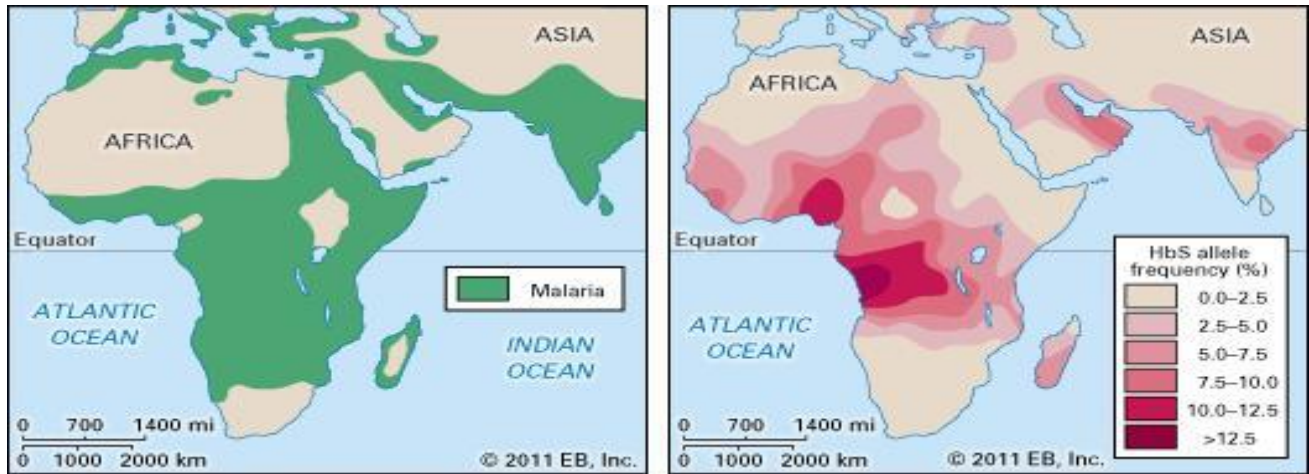


Figure 1: The distribution of malaria and the distribution of sickle cell anaemia overlap in areas of Africa, Southern Asia, and the Mediterranean. The persistence of the HbS gene, which causes sickle cell anaemia, has been explained by the fact that heterozygous persons are resistant to malaria. (adapted from <http://media-2.web.britannica.com/eb-media/84/126284>).

Sickle Cell Nephropathy

Sickle cell nephropathy (SCN) is a frequent complication in a large proportion of patients with this disease. This renal complication could affect both the glomerular and tubular functions; the clinical manifestation will depend on which function is predominantly compromised, but ultimately both dysfunctions end in renal failure (Aloni et al., 2014; Abdu et al.,2011 and Guasch et al., 2006). The pathophysiology of SCN has not been fully elucidated. Falks et al. (1992) have proposed a glomerulopathy (abnormalities of the glomeruli) as the basis for the development of SCN. The hypoxic and hyper-osmolar condition of the renal medulla in SCA predisposes the red cells to undergo sickling, this result in vaso-occlusion within the vessel. In response to this, renal prostaglandin synthesis increases, resulting in vasodilatation of the afferent arteriole and glomerular hypertension, this in turn lead to the gradual loss of nephrons. The remaining nephrons undergo hypertrophy and glomerulosclerosis (scarring of the glomeruli). This

affects the selective permeability properties of the kidney and consequently large molecules, such as glucose, protein passes freely through the previously restrictive pores of the glomeruli. The early sign of such renal damage is the appearance of small amount of albumin in the urine known as microalbuminuria (Yee et al 2011).

Microalbuminuria is an important preclinical indicator of early glomerular damage, a stage usually devoid of clinical signs and symptoms. It has been identified as a marker of renal and cardiovascular complications not only in diabetes and hypertensives, but also in the healthy population (Yagouide and Akani 2011). It has also been shown to be a marker of early glomerular injury in patients with SCA. The aim of this review is to determine the prevalence and associated risk factors of microalbuminuria, and the clinical significance in patients with sickle cell anaemia.

Microalbuminuria: Definition and Laboratory detection



In the healthy individual, the urinary content of albumin is between 10-15mg of the total protein content of 150mg per day. Microalbuminuria (MA) is defined as an albumin excretion of 20 to 200µg/min or 30-300mg/day (Chronolab, 2009). The term 'Microalbuminuria' is misleading in the literal context, because it denotes small amount of albumin excretion, and not the passage of small sized molecules of albumin. Microalbuminuria can be detected in the laboratory using either quantitative or semi quantitative techniques. The quantitative method is based on the reaction between albumin and antibody to human albumin and includes radioimmunoassay (RIA), radio immunodiffusion, ELISA and immunoturbidimetry. The individual quantitative assays have advantages and disadvantages, but overall, they all have a high sensitivity and specificity rates (Chronolab, 2009). The choice for a particular method will depend on technical skills and availability. The semi quantitative assays are ideal for screening purposes and include test strips, latex agglutination test (Inhibition test), micro-albumin test and micral test. The test strips are suitable for use in clinics during routine follow-up, and can be combined with a urine analyser to calculate the ratio of albumin and creatinine excretion (Price, 2009).

The concentration of albumin in urine is determined by two factors; the concentration of the urine and the amount of albumin excreted, thus a diluted urine may give a falsely low result, this is particularly important in SCA, which is frequently complicated by hyposthenuria (inability to concentrate urine), resulting in the passage of diluted urine (Pham et al., 2000). To correct for this dilutional effect, a spot urine sample corrected for creatinine excretion is the preferred sample; alternatively, 24hr urine collection or timed-overnight urine sample can be used, however, these last two methods are not patient friendly (Pagana, 2006).

Prevalence of Microalbuminuria in SCA

Several studies have shown an increasing trend in the prevalence of MA with increasing age (Eke et al., 2012; Aygun et al., 2011; Becton et al., 2010 and Datta et al., 2003). In their study to evaluate the prevalence of MA in children less than 14 years of

age, Datta et al. (2003) reported 19.2% in the SCA group. Other studies in children, reported prevalence rates of 18.5%, 15.9% and 15.5% respectively (Eke et al., 2012; Aygun et al., 2011 and Becton et al., 2010). In comparison, studies that included both children and adolescents, reported a higher prevalence. In two of such studies carried out in children 2-18years, the authors reported prevalence rates of 26.5% and 28.2% respectively for microalbuminuria (Mawanda et al., 2011; Dharnidharka et al., 1998). In addition, Dharnidharka et al. (1998) noted a sharp increase from a prevalence of 26.5% to 46% when the age range of the subjects' population was increased from the initial 2-18years to 10-18years.

Consideration of the prevalence of MA in the adult's population showed a further rise from the paediatric value (Day et al., 2012; Asnani et al., 2011; Mawanda et al., 2011; Ataga et al., 2010; Haymann et al., 2010 and Aoki et al., 1990). The age range for most of the studies was wide at 20 to 27yrs. Guasch et al. (2006) and Haymann et al. (2010), reported 68% and 60% respectively for the prevalence of MA in adults with SCA. Similarly, Aoki and Saad (1990) found a prevalence of 40%. Reports from other studies showed slightly lower values than this later study (Day et al., 2012; Ataga et al., 2010). It is apparent from these reports that MA becomes increasingly prevalent with advancing age, indicating that SCN begins from childhood and progresses into adulthood. The consistent and similarity of the results within the different age groups suggest that there is no significant regional variability. The progressive and rising prevalence of MA with age underscores the importance of early identification of risk factors associated with its development and progression.

Risk Factors for Microalbuminuria in SCA

From above reports, age appeared to be the single most independent variable associated with the development of MA. Other factors that have been associated with MA do so to a variable degree; these include glomerular hyperfiltration, blood pressure, gender, haemoglobin concentration, white blood cell count and markers of haemolysis (LDH, reticulocytes, AST), these are considered below:

Glomerular Hyperfiltration

This phenomenon has been shown to occur early in life in individuals with SCA. The exact mechanism is unknown, and it has been suggested that it may be part of the haemodynamic adaptations that occur in response to glomerular hypertension in sickle cell anaemia (Chronolab, 2009). It is characterized by a GFR of above 140ml/min/body surface area. A high GFR would have been considered beneficial to patients with SCA, however, glomerular hyperfiltration is associated with the processes involved in glomerulosclerosis and development of renal failure (Pham *et al.*, 2000). In studies demonstrating the association of hyperfiltration and MA, some of the authors have combined both direct measurement (mGFR) and estimated (eGFR) measurement for the determination of GFR. Direct measurements provide better and accurate assessment of GFR, however it is not routinely available, and may not be popular because such techniques use various forms of radioactive substance for labelling.

In three different studies where the authors combined both mGFR and eGFR measurements, there was concordance in the prevalence of hyperfiltration and a significant correlation with MA. The GFR was higher in both male and female subjects with SCA compared with normal controls and correlated positively with albumin excretion (Day *et al.*, 2012; Eke *et al.*, 2012 and Dharnidharka *et al.*, 1998). In addition, the reports also demonstrated the phenomenon of high GFR in children with progressive decline into adulthood; the value for GFR in children compared with adults was 154ml/min/1.73m² vs 133ml/min/1.73m² respectively (Aygun *et al.*, 2011). Other studies using estimated GFR only, also found correlation between MA and hyperfiltration (Haymann *et al.*, 2010; Dharnidharka *et al.*, 1998). However, results obtained from estimated GFR yields falsely higher values; this is because most of the formulas used for estimated GFR utilised creatinine measurement and clearance; creatinine secretion into the tubules makes it a less reliable marker of renal function.

Blood Pressure

In the non-sickle cell population, elevated blood pressure (BP) has been shown to strongly correlate with the development of chronic renal failure, alongside other risk factors like diabetes, obesity and metabolic syndrome (Najaf *et al.*, 2010). Various studies have confirmed the association of high BP and MA in patients with SCA (Aygun *et al.*, 2011; Thompson *et al.*, 2007). In a report in children with SCA, the authors found positive correlation between high BP and MA; they inferred that this may be a predictor for the development of SCN and other secondary complications (Becton *et al.*, 2010). Furthermore, a higher mean arterial pressure in subjects with HbSS was shown to be a significant predictor of MA (Asnani *et al.*, 2011). In variance to reports associating high BP and MA, a lower than normal systemic BP in patients with SCA compared with the controls have also been observed by other authors. Unlike in non-sickling disorders where the BP levels increase with the developments of microalbuminuria, in some group of SCA patients this may not be the case (Imuetinyan *et al.*, 2011 and Guasch *et al.*, 2006). There is evidence of chronic nitric oxide (NO) activation (a potent vaso dilator) in patients with SCA, confirmed by increased urinary excretion of NO metabolites when compared with the non-anaemic control subjects, additionally, there is decrease reaction of the peripheral vessels in response to blockade of the NO system in patients with SCA (Guasch *et al.*, 2006). The authors suggested that this could be the cause of resistance to hypertension in this group of individuals. The lower than normal BP in patients with sickle cell disease has also been attributed to the combined effects of cardiac dilatation, increase preload, decrease peripheral resistance and reduce afterload as result of the chronic anaemia in SCA (Imuetinyan *et al.*, 2011).

Gender

The association of gender and MA have shown less variation compared with other variables. Review of literature showed a trend characterized by high rates of MA in females with SCA (Eke *et al.*, 2012; Imuetinyan *et al.*, 2011 and Dharnidharka *et al.*, 1998), however none of these reports reached



significant value. Majority of the authors attributed this finding to the high frequency of urinary infection in the general population of females, and the added effect of increased susceptibility to infections in patients with SCA. Despite these findings, there was no established causal relationship between female gender and the risk of MA. In addition, there is no documented evidence indicating the prevalence of sickle cell nephropathy to be higher in the female population.

Haemoglobin and White Blood Cell Counts

Amongst the haematological parameters measured in various studies, low haemoglobin (Hb) was consistently associated with MA. The association between low Hb and MA reached significant level in majority of the studies (Day *et al.*, 2012; Eke *et al.*, 2012). It was proposed that the on-going sickling within the kidney due to medullary hypoxia and ischemia may be a factor; however, it was difficult to establish a cause-effect relationship between low Hb and MA, given that SCA is characterized with red cells that have a reduced lifespan, owing to chronic haemolysis. Increase white blood cell count (WBC) in patients with SCA, independently predicts severity and mortality, and significant association between MA and high WBC count ($p=0.003$) has been demonstrated (Asnani *et al.*, 2011; Hagar and Vichinsky 2008). A possible association between inflammation and sickle cell nephropathy has been suggested, especially given the benefit of decrease in the progression of SCN following reduction in WBC counts using drugs like Hydroxyurea.

Markers of Haemolysis

A report by Day *et al.* (2012) showed a significant association between MA and various markers of haemolysis, these includes, reticulocytes ($p=0.02$), Hb ($p < 0.0005$), LDH ($p < 0.0001$) and bilirubin ($p < 0.0001$); they inferred from these results that SCN is associated with a haemolytic sub-phenotype of SCA (Day *et al.*, 2012). On the other hand, Asnani *et al.* (2011) have reported no association with any of the haemolysis markers in their study (LDH, AST). Similar reports of lack of association between MA and markers of haemolysis have been documented in other studies (Aygun *et al.*, 2011;

Ataga *et al.*, 2010 and Guasch *et al.*, 2006). The dissimilarities from above reports could be attributed to the differing phenotypes of the subject recruited for the studies. Patients with SCA can be classified into one of two groups - a haemolytic or vaso-occlusive phenotype, depending on the predominant clinical profile of the individual patient.

Clinical Significance of Microalbuminuria in SCA.

Understanding the natural progression of MA in patients with SCA may provide more insight of its clinical significance. Currently, no longitudinal study has been carried out to determine the stages involved from the detection of MA to the development of renal failure. Guasch *et al.* (2006) have attempted to elucidate this progression by putting forward a hypothesis which suggests that sickle cell glomerulopathy evolves through five graded stages of albuminuria; the first stage is characterized by normal albumin excretion, the second and third stages correspond to microalbuminuria and macroalbuminuria respectively, with preserved GFR; a fourth stage of macroalbuminuria and progressive renal insufficiency and a fifth stage of end stage renal disease (Guasch *et al.*, 2006). Given the high prevalence of MA in SCA, identification of the associated risk factors can allow for early intervention, especially considering the limited treatment options available in established renal failure, early screening using MA can be employed to identify high risk groups. Currently, angiotensin converting enzymes inhibitors (ACE I) are used to decrease protein excretion and retard the progression of renal damage. Falk *et al.* (1992) observed in their study that, following administration of ACE I in patients with SCA for six-month duration, there was a rapid and reversibly decline in protein excretion (Falk *et al.*, 1992). They also noted the decrease in proteinuria was not accompanied by changes in renal haemodynamic parameters, emphasizing the fact that glomerulosclerosis is the underlying cause of proteinuria.

In a randomized, double blind placebo-controlled trial in 22 subjects with SCA and MA, Foucien *et al.* (1998) reported that, the mean absolute and

percentage change in MA was significant between the control group and placebo group ($p < 0.01$), they also documented a significant decrease in diastolic blood pressure between both groups ($p < 0.01$) (Foucen et al., 1998). In a third study that evaluated the effect of ACE I, a reduction in the level of MA following six months of treatment in six out of the eight patients was reported, however the MA returned back to pre-treatment levels following discontinuation of treatment; Furthermore, the study could not establish if ACE I can delay the progression of renal failure in patients with SCA (Aoki and Saad, 1995). The results from these

reports are promising, however the studies are small and old, while others have used proteinuria as the independent variable, it is therefore difficult to draw conclusion of the exact role of such agents in retarding the progression of renal failure. Another drug gaining interest in SCN is Hydroxyurea. In their report, Mckie *et al.* (2007) noted that MA excretion normalized in 44% of patients who received Hydroxyurea and in 55% of patients who received ACEI; they suggested that combination of Hydroxyurea and ACEI may be beneficial for MA and proteinuria (Mckie *et al.*, 2007).

Table 1: Summary of literatures examining microalbuminuria in sickle cell anaemia patients

Reference	Number of Patients	Prevalence of Microalbuminuria	Average age (years)	Statistical sig. Factors
CHILDREN				
Datta et al., 2003	64	19.2	Up to 14	↓WBC, female
Aygun et al., 2011	85	15.9	children	↓WBC, ↑BP ↑GFR
Becton et al., 2011	90	16	children	↓Hb, ↑BP
Eke et al., 2012	200	18.5	11.2	↓Hb, female gender
CHILDREN/TEENS				
Dharnidharka et al., 1998	102	26.5 46	2-18 10-18	-
Yee et al., 2011	261	23	2-21	↓ Hb, ↑GFR
Imuetinyan et al., 2011	69	20.3	1-16	Gender(F)& Age
Mohtat., 2011	42	10	2-21	-
Mwanda., 2011	305	28.2	2-18	↓ Hb, ↑GFR
ADULTS				
Guasch et al., 2006	184	68	adults	↑BP
Thompson et al., 2007	65	26	adults	↑BP, ↑GFR
Ataga et al., 2010	73	32.9	adults	-
Haymann et al., 2010	280	60	“	↓Hb, ↑GFR
Asnani et al., 2011	122	25.9	“	↑WBC, ↑BP ↓Hb, ↓retics
Day et al., 2012	260	37	17-70	↑LDH, Retic, Bilirubin, GFR & Hb

WBC: white blood count; Hb: haemoglobin; BP: blood pressure; LDH: lactate dehydrogenase; ASAT: alanine amino transferase; Retic: reticulocytes; GFR: glomerular filtration rate.



Conclusion

There is ample of evidence indicating the prevalence of microalbuminuria is high in patients with SCA, and it is associated with both clinical and laboratory variables such as low Hb, hyperfiltration, high BP and high WBC and markers of haemolysis. Screening for MA in patients with such risk factors is widely recommended as a timely intervention. Therapeutics trials with Hydroxyurea, though not yet in routine clinical use, have shown promising results. However more studies are required to establish if this drug can retard the progression of microalbuminuria to renal failure.

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