Could sickle cell trait be a predisposing risk factor for CKD?

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Whilst the needs of individuals with sickle cell disorder (SCD) may be apparent, individuals with sickle cell trait (SCT) are generally reassured that their health will not be affected by their carrier status. Renal failure is a recognized complication of SCD; however, little is known concerning the relationship between SCT and the development of chronic kidney disease (CKD). In this short article, we discuss the rationale for further studies into this area, which we believe could impact on global public health recommendations.

Sickle cell trait

SCD is a common and serious inherited blood disorder affecting ~300 000 live births globally per year [1]. The international burden of SCD is in the order of millions and is particularly prevalent in Sub-Saharan Africa. It occurs as the result of a substitution of valine for glutamic acid at the sixth amino acid position of the beta globin gene on the short arm of chromosome 11. For the full disease to be manifested, this mutation must be present on both inherited alleles. SCT is the heterozygous form of the condition and is present in 8% of African Americans (2.5 million individuals) and potentially as many as 40% of West Africans [2–4]. With global migration patterns changing, the burden of this carrier state is on the increase in Europe and it is estimated that ~1% of the total European population now carry a haemoglobinopathy gene, the majority of which code for SCDs [5]. For this reason, many countries across Europe have introduced neonatal screening programmes for early detection and hence treatment of haemoglobinopathies [6].

The complications of SCD are well recognized and can affect any organ in the body. Although individuals with SCT are not thought to have a reduced life expectancy, they do have 30–40% of their haemoglobin as the sickle variant, which does confer a risk for certain conditions. Metabolic or environmental changes such as hypoxia, acidosis, dehydration, hyperosmolality or hyperthermia may transform silent SCT into a syndrome resembling SCD with vaso-occlusive crisis due to an accumulation of low deformable red blood cells in the microcirculation [7,8]. In keeping with this, there are many reported cases of acute complications in people with SCT such as splenic infarction, rhabdomyolysis, heat stroke, acute renal failure and sudden death [9–14]. These events occur under conditions of extreme physical stress and are often attributed to vaso-occlusive crises, suggesting that, although SCT is often quiescent, it may not always be benign.

Sickle cell trait and the kidney

Renal impairment is a complication of SCD affecting 4–20% of patients [15–17]. As a consequence of the long vasa recta and the countercurrent exchange system, the healthy kidney is a site of relative hypoxia and is, therefore, an environment that encourages sickling of red blood cells and vaso-occlusion in susceptible individuals. In keeping with this, microangiopathic studies have demonstrated that the intrarenal medullary blood vessels are significantly damaged in both SCD and SCT, though to a lesser degree in the latter [18]. Macroscopic haematuria occurs in patients with both SCD and SCT and, in one study, accounted for 4% of all hospital admissions in African Americans with SCT [19]. About 50% of cases are due to papillary necrosis which is generally self-limiting but which can lead to prolonged frank haematuria, obstruction from sloughed papillae and infection [20]. A more rare but devastating complication of carrying at least one sickle cell gene is renal medullary carcinoma. This was first reported in 1995 in a case series of 34 patients, 33 of whom had SCT. It is an aggressive tumour that is almost always metastatic at presentation, universally fatal and primarily affects young people from early childhood to around age 40 [21,22]. Chronic effects on kidney function are also detectable in patients with SCT. Hyposphrenuria is common in children with SCD and is usually irreversible by the age of 10 with most adults being unable to concentrate their urine to >450 mOsm/kg when deprived of water. Although not so severe, this phenomenon is also
apparent in people with SCT and can lead to dehydration under conditions of extreme heat or exercise, probably contributing to the cases of sudden death reported under these conditions [23]. There is, however, a paucity of data examining the relationship between SCT and CKD. One study undertaken recently in the USA demonstrated a 50% higher prevalence of SCT amongst an end-stage renal disease (ESRD) population of African Americans compared to that inferred from the newborn haemoglobinopathy screening programme, suggesting that it may indeed be a risk factor for developing CKD [24]. The mechanism by which SCT may contribute to the progression of CKD is probably multifactorial. Repeated localized areas of sickling and venous occlusion leading to chronic microvascular damage could conceivably lead to chronic hypoxia and tubulointerstitial fibrosis. It is also possible that SCT, when coexisting with other conditions that affect the renal microvasculature, may act synergistically to accelerate renal damage. In keeping with this, microalbuminuria and proteinuria have been reported to be more prevalent in male Type 2 diabetics with SCT than in those with normal haemoglobin [25]. Similarly, hypertension may also act in concert with SCT to impair microvascular function leading to progression or acceleration of CKD.

**Chronic kidney disease**

CKD is a significant health care issue worldwide with as many as 35% of the population over 64 affected [26,27]. Though this reflects a group of people who are largely unknown to renal services, it has resulted in an ESRD prevalence of 1626 p.m.p. in the US and 746 p.m.p. in the UK, which has been incrementing year on year, particularly in the ethnic minority populations [28, 29]. The cost of renal replacement therapy represents a huge financial burden to governments worldwide and it is recognized that global renal services at the current level are insufficient to cope with early referral of all patients with CKD and, indeed, it would be unnecessary as most remain stable for years [30]. However, there is a need to identify those patients who are at greater risk of developing progressive disease and to target these people for early referral to specialist services for appropriate and timely intervention and risk profile modification.

**Sickle cell trait and transplantation**

There is no clear policy either in Europe or the US on the use of live donors with SCT for kidney transplantation. One recent study in the US used an original questionnaire to determine local policies on this issue and discovered that 83% of transplant centres had no policy to screen for this condition. Although 37% of centres said they would exclude donors with SCT always or most of the time, 19% reported that they would not [31]. The UK guidelines on living donation suggest testing for the trait ‘where indicated’, but do not discuss how to manage a positive result [32]. If SCT does confer a risk of developing CKD, this will clearly have implications for the donor and potentially the recipient.

Given the high prevalence of SCT, further investigation of the relationship between this common genetic condition and the development of CKD is warranted. If SCT is a risk factor for developing CKD later in life, this could significantly influence recommended care and referral patterns worldwide.

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**References**

When to start chronic dialysis: tunnel vision induced by numbers?

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In this issue of NDT, Hwang et al. [1] report the retrospective analysis of the relation between estimated glomerular filtration rate at the start of dialysis (start eGFR) and outcome. The conclusion is that a higher start eGFR is related to higher mortality, as was also found in previous cohort studies [2–5]. Of more interest, as in a recent analysis of the REIN study [6], a higher start eGFR was associated with higher comorbidity [1]. Thus, the Hwang paper further fuels the heated debate on the timing of start of dialysis in several ways. The most prevalent ‘en vogue’ answer to the question of when it is best to start dialysis is — early start is detrimental. This viewpoint is the complete opposite of the previous mantra claiming that an early start improves outcome. The most scientifically honest answer is rather — we simply do not know.

In this era of ‘evidence-based medicine’, this might seem a paradoxical point of view, when taking into account that an entire set of studies [2–4] reached a definitive and unanimous conclusion, in disfavour of an early start. This editorial lists some reasons why we should exercise caution in regard to the current line of thinking, taking the Hwang paper [1] as an example.

Maintaining the same logic until the bitter end?

There is a worrisome, but logical, consequence to all the retrospective studies on start eGFR published so far: they all find a linear inverse association between start eGFR and mortality, with not a single indication of a J shape. Consequently, we should either accept the data and delay starting dialysis until patients become anuric or accept that there is something wrong with the data and question the conclusions. Patients die of uraemia before they become anuric unless they are dialysed, which is in contradiction with the data as currently presented. In addition, several registries report a historical trend towards starting dialysis at higher eGFRs over the last decade, and at the same time, there is also a decline in mortality, which again conflicts with the interpretation that a higher start eGFR is deleterious [7,8].

A second observation is at least as puzzling: if physicians use eGFR as a parameter to start dialysis, why then is there such a large variability among start eGFR values in...