Minireview

Sickle cell disease as an accelerated aging syndrome

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Impact Statement

Sickle cell disease was the first genetic disease to be described and is one of the most prevalent genetic diseases among individuals of African ancestry. However, our understanding of this disease and its associated pathophysiology is still limited. This review described sickle cell disease in the context of aging and shows that sickle cell may result in structural and molecular changes that have been described in aging. And since the overwhelming majority of individuals with sickle cell disease are below the age of 50 years, we argue here that sickle cell disease is indeed an accelerated aging syndrome.

Abstract

Sickle cell disease (SCD) is characterized by vaso-occlusion, hemolysis, and systemic manifestations that form the hallmark of the disease. Apart from morbidity, SCD is also associated with increased mortality and decreased quality of life. Aging is a natural phenomenon that is associated with changes at cellular, tissue, and organ levels, in addition to the loss of physical fitness, increased susceptibility to diseases, and a higher likelihood of mortality. Some of the cellular mechanisms involved in normal (or physiological) aging include abnormalities of sphingolipids (ceramides) and reduced length of the telomere. These changes have also been documented in SCD. Cellular, organs, and physical manifestations of SCD resemble an accelerated aging syndrome. Sickle erythrocytes also acquire morphological features similar to that of aged normal erythrocytes and are thus picked up early by the macrophages for destruction. Brain, kidney, heart, innate and adaptive immune system, and musculoskeletal system of patients with SCD exhibit morphological and functional changes that are ordinarily seen in the elderly in the general population. Stroke, silent cerebral infarcts, cardiomegaly, heart failure, pulmonary hypertension, nephropathy with proteinuria, osteopenia, osteoporosis, osteonecrosis, gout, and infections are exceedingly common in SCD. In this review, we have attempted to draw parallels between SCD and accelerated aging syndromes.

Keywords: Accelerated aging, sickle cell disease, aging, organ damage, hematology

***Experimental Biology and Medicine* 2022; 247: 368–374. DOI: 10.1177/15353702211068522**

Introduction

Globally, there are about 25 million people affected by sickle cell disease (SCD), with 75% living in sub-Saharan African.[1] The evolution and distribution of SCD overlap with areas of a high prevalence of severe falciparum malaria.[2] The relationship between SCD and malaria can best be described as a balanced polymorphism, and it underscores the role of malaria as the gene driver of this mutation.[3] Nevertheless, as a result of migration and interracial marriages, SCD is emerging as a common genetic disease in Europe and the Americas.[4] It is also found in the Indian subcontinent and the Middle East, although the clinical presentation may be less severe because of associated thalassemia and considerably favorable Arab-Indian haplotype when compared to severer Bantu, Benin, and Senegal haplotypes.[5]

SCD is the first molecular disease identified by humankind, with an autosomal recessive pattern of inheritance. The pathobiology of SCD starts with a point mutation whose translational product results in the replacement of a hydrophilic amino acid (glutamic acid) with a hydrophobic amino acid (valine) at the sixth position of the beta globin chain.[6]

There are various phenotypes of SCD, which share a commonality in the sickling of erythrocytes under low oxygen concentration with associated vaso-occlusion and/or hemolysis.[6] The current paradigm broadly classified the clinical phenotypes of SCD into hemolytic/endothelial dysfunction and vaso-occlusive/hyperviscosity.[7,8] This classification is built on the premise of low hemoglobin and high hemolytic markers or high hemoglobin and low hemolytic markers, in addition to the spectrum of morbidities associated with either hemoglobin level or hemolytic markers.[7,8] The spectrum of morbidities defining SCD clinical phenotypes consists of systemic manifestations associated with both acute and chronic complications in several organs of the body.[6] The heterogeneity

seen in the spectrum of morbidities could be related to the differences in the level of disease modifiers, including sickle hemoglobin (HbS) and fetal hemoglobin (HbF) concentrations, red cell hydration, oxygenation, haplotypes, and so on.

Aging is a natural process with a hallmark of gradual deterioration of physiological and physical functions, morphological changes, and loss of fitness or energy. It is also associated with an increased risk of diseases and a higher likelihood of mortality.[9] Accelerated aging is a state of fast decline in physical, biochemical, physiological, and organ functions, which is mostly associated with genetic, metabolic, or chronic diseases, and could lead to early death.[10] Although the underlying mechanisms of accelerated aging lie at the molecular and cellular levels, organ damage/failure is a critical determinant of aging.[10] SCD often presents with multiple organs complications,[11] which mimics an accelerated aging syndrome, and manifests with endothelial dysfunction as one of the cardinal features. In a prospective cohort of adults with SCD (median age 25.5 years), the prevalence of multiple end-organ complications was 59.3%, and the number of end organs affected was significantly associated with mortality.[11] Therefore, considering the dramatic decline in organs functions at a relatively younger age, the calendar age of patients with SCD could be misleading when compared to the biological/physiological age.[9,12] This review intends to provide perspectives on the novel concept of SCD as an accelerated aging syndrome.

Methods and search strategy

We identified articles to be included in this review via search engines (PubMed and Google Scholar). We used the following combination of keywords: accelerated aging AND sickle cell disease OR sickle cell telomere OR sickle cell ubiquitin–proteasome system OR sickle cell sphingolipids OR sickle cell immune system aging OR sickle cell organs aging. The publication period was expanded, to include everything published until September 2020. We also reviewed the bibliographies of the articles that were selected for a full review to identify more articles for inclusion in this review. A second search was conducted to include publications from September 2020 to October 2021. The second search was to ensure that we included any new publications that were not included in our initially submitted manuscript and/or were suggested/recommended by the reviewers. We present a detailed discussion of the results of this article search below. A summary of the most relevant manuscripts is also presented in Table 1.

SCD exhibits cellular and molecular mechanisms of accelerated aging

Several genetic and metabolic pathways have been implicated in the natural aging process. A study in eukaryotes has demonstrated that knocking down of the longevity assurance gene 1 (LAG1), which encodes enzyme ceramide synthase, increases the lifespan of *Saccharomyces cerevisiae*.[13] This observation provides a clue about the role of sphingolipid metabolite (ceramide) in the aging process. Reduction in glucosylceramide plays a role in the age-dependent deterioration of immune functions of CD4+ T-cells.[14] Recent studies among children with SCD, has reported low serum ceramide as well as high phosphated ceramide and sphingosine levels,[15] similar to what is observed in aging. Apart from these, natural aging has been linked to increased chemokines and proinflammatory cytokines (such as tumor necrosis factor (TNF) alpha) in cells and tissues, and this interferes with the activity of telomerase.[16] Similar effects of these cytokines and chemokine on accelerated aging have also been reported in a state of magnesium deficiency. Magnesium deficiency induces the generation of free radicals, and this can damage the DNA, and possibly downregulates telomerase to interfere with cell growth and division.[17] Low plasma levels of ionized magnesium and red cell magnesium were reported in a significant proportion of patients with SCD.[18] Magnesium seems to act as a vasodilator and a calcium channel blocker in the heart, and thus, magnesium deficiency is reportedly associated with hypertension, cardiovascular diseases, and atherosclerosis.[17] In SCD, magnesium deficiency could also lead to red cell dehydration; an effect that increases the rate of sickling and hemolysis.[18] The cumulative effect of these changes predisposes the patients to morbidities such as stroke, pulmonary hypertension (PH), and leg ulcers.[7]

Telomeres are tandem repeats of nucleotides' sequences located at the end of chromosomes for stability.[16] These nucleotides' caps of chromosomes shorten in length with each cell division, eventually limiting the number of cell divisions. Hence, the length of telomere is an important determinant of the cell cycle, growth, and aging. Therefore, maintenance of telomere length is made efficient by the normal activity of telomerase.[16] Persons with SCD have been reported to have shorter telomere length compared with chronological age-matched healthy control, and this correlates with the disease severity (more in HbSS than HbSC) and inflammation.[19,20] Therefore, in the setting of the combined effects of magnesium deficiency-related impairment of telomerase activity and the documented shorter level of telomeres associated with SCD itself, we postulate that SCD may be viewed as accelerated aging at the molecular level.

Another mechanism of regulating aging is through maintenance of protein quality. Damaged proteins are polyubiquitinated as a mechanism for recognition by the 19s regulatory proteasome core and subsequent action of the 20s catalytic proteasome core.[21] The catalytic proteasome core has caspase-, trypsin- and chymotrypsin-like activities.[21] Accumulation of low-quality proteins results from a failure of the ubiquitin–proteasome system to flag misfolded proteins for degradation in the lysosome.[22–24] This failure of the cells to degrade misfolded (low quality) proteins has been shown to fast-track aging at the cellular and tissue levels.[22-24] SCD also exhibits dysfunction of the ubiquitin–proteasome system,[24] hence giving credence to the disease as an accelerated aging syndrome. There are also epigenetic mechanisms involved in the aging process; however, these have not been well-studied in SCD and future studies may show that the changes observed in aging are also similar to those seen in patients with SCD, who might be significantly younger in chronological age.[25]

Sickle erythrocytes exhibit features of accelerated aging

The average life span of normal erythrocytes is 110 ± 10 days; however, sickle erythrocyte's lifespan is reduced to barely

Table 1. Summary of studies on cellular, tissue, and organ characteristics of aging in sickle cell disease compared to the general population.

	Aging-related features	Sickle cell disease–related features	Citations
1. Sphingolipid metabolism	Ceramide is associated with aging.[13] Increased acid sphingomyelinase plays a role in age-related neuroinflammation and neurodegenerative changes.[50,51]	Compared to healthy controls, SCD is associated with reduced serum ceramide.[15]	Sinclair *et al.*[13] Alessenko[50] Park[51] Aslan[15]
2. Telomere length	Telomere length is a determinant of the cell cycle, growth, and aging. Shorter telomere indicates aging.[16]	Patients with SCD have shorter telomere than healthy controls. The telomere length also correlates negatively with the disease severity (shorter in HbSS than HbSC) and inflammation.[19]	Aubert[16] Colella[19]
3. Protein quality maintenance	Accumulation of proteins of low quality occurs due to failure of the ubiquitin–proteasome system to flag misfolded proteins for degradation in the lysosome, which is shown to fast-track aging at the cellular and tissue levels.[22]	Sickle cell disease exhibits dysfunction of the ubiquitin–proteasome system. Cellular level of polyubiquitinated proteins was high in SCD patients compared to healthy controls and hydroxyurea-treated patients.[24]	Carrard[22] Warang[24]
4. Magnesium homeostasis	Magnesium deficiency predisposes to the generation of free radicals, which could damage DNA and possibly downregulates telomerase. In a state of deficiency, magnesium is associated with hypertension, cardiovascular diseases, and atherosclerosis.[17]	Magnesium deficiency leads to red cell dehydration, which predisposes to increased sickling and hemolysis[18] with associated morbidities such as stroke, pulmonary hypertension, and leg ulcers.	Altura[17] Antwi-Boasiako[18]
5. Red cell characteristics	Features of red cell aging such as high density, changes in band3, increased membrane-bound IgG, recognition by reticuloendothelial system for destruction after a life span of averagely 120 days.[23,24]	Sickle erythrocytes harbor morphological and functional characteristics of aged normal red cells at a young age, such as high density; changes in band3, increased membrane-bound IgG, and externalization of phosphatidylserine enabling recognition by the reticuloendothelial system after a life span of averagely 30 days.[26,27]	Franco[23] Yasin[26] Bosman[27]
6. Organs and systems changes: Brain Pulmonary system Musculoskeletal system Renal system Immune system	Ischemic stroke occurs in elderly population with atherosclerosis, and less commonly in young adult. Age- and neurodegenerative disease–related cognitive deficits are common. Global prevalence of pulmonary hypertension is put at 1%, but is as high as 10% in aged population ⩾65 years. Aging-related bone loss and osteoporosis often leading to fracture or arthritis.[40] Kidney changes in elderly include glomerulosclerosis and tubulofibrosis. Glomerular filtration rate declines steadily from 40 years in normal individuals.[55] Immunosenescence predisposing aged population to infections.[62] Zinc deficiency is common in aged people and causes lymphophenia.[62]	Ischemic stroke occurs in about 11% of children and adolescents as a result of endothelial dysfunction.[49] Neurological injuries- and SCD-related cognitive deficits are common.[47] Pulmonary hypertension prevalence in SCD is averagely 10%. It is associated with low apolipoprotein A (APO-A) and high polyubiquitin, both of them are cellular markers of aging.[32] Loss of bone mineral density and osteoporosis of vertebral bone.[41] Advanced osteoarthritis related to avascular necrosis.[40,41] SCD is associated with glomerular hypertrophy, glomerulosclerosis, and fibrosis.[54] Glomerular filtration rate initially starts with hyperfiltration and steadily declines from childhood. Hyposplenism and functional asplenia,[60] including zinc deficiency predisposing patients with SCD to infections. Zinc deficiency is common SCD.[61]	Schatz[49] Prussien[47] Anjum[32] Ballas[40] Farook[41] Nath[54] Schlanger[55] Brousse[60] Booth[61] Burkle[62] Haase[63]

SCD: sickle cell disease.

20 days due to morphological changes culminating with both chronic intravascular and extravascular hemolysis.[23,26] Polymerization and associated sickling cause injuries to sickle erythrocytes. These injuries damage the membrane to cause perturbation of the lipid bilayer by exposing phosphatidylserine.[26] Sickle erythrocytes harbor morphological and functional characteristics of aged normal erythrocytes, such as high density, changes in band3, and increased membrane-bound IgG.[27] These changes (typically observed in aged erythrocytes) seen in relatively young sickle erythrocytes are features that support the postulation of SCD as an accelerated aging syndrome.[27] Eventually, the prematurely aged sickle erythrocytes are picked by the macrophages (which carry phosphatidylserine receptors) in the reticuloendothelial cells and destroyed.[23] Often, these damaged sickle erythrocytes undergo defragmentation within the vessels and released cell-free hemoglobin, which mops up haptoglobin, nitric oxide (NO), and hemopexin.[7] SCD is also associated with dysfunction of ubiquitin–proteasome system.[24] The cellular level of polyubiquitinated proteins was shown to be high in patients with SCD when compared to healthy controls and hydroxyurea-treated patients with SCD.[24] Perhaps the comparatively low levels of polyubiquitinated proteins reported in patients with SCD treated with hydroxyurea could be attributed to the antioxidant effect of the drug.[24]

Hypothetically, as a result of accelerated aging, we infer that a chronological day-5 sickle erythrocyte is akin to physiological age of approximately 30-day old normal erythrocyte. Essentially, based on life expectancy, the aging process

of sickle erythrocyte could be sixfold faster than normal erythrocytes.

Organs damages observed in aging form the bedrock of clinical phenotypes of SCD

A couple of decades ago, SCD was considered primarily a pediatric disease (especially in low resource settings) due to high childhood mortality.[28] However, recent advances in the care of patients with SCD have improved the childhood survival with most of the children born in high-income countries living up to adulthood.[28] As more patients with SCD survive into adulthood, there would be increased clustering of SCD-related organ damages.[11]

The pathophysiology of SCD-related organ damages is mainly a consequence of repeated vaso-occlusion or chronic hemolysis.[7,29] The repeated vaso-occlusion is associated with hyperviscosity and tissue ischemia–reperfusion injury, which cumulatively result in various complications and organ dysfunctions.[29] Complications such as acute chest syndrome, osteonecrosis, and retinopathy are considered to be vaso-occlusive/hyperviscosity subphenotypes of SCD.[7] However, chronic intravascular hemolysis releases cell-free hemoglobin, which mops up the potent vasodilator NO and generates heme.[6] NO depletion and reactive oxygen species from heme generation drive the endothelial dysfunction/vasculopathy and sterile inflammation, respectively.[7] Hemolysis is also associated with release of arginase and asymmetric dimethylarginine from lysed erythrocytes leading to reduced availability of arginine (a precursor of NO) and inhibiting endothelial nitric oxide synthase (NO3).[7] A combined effect of these cellular mechanisms favors vaso-constriction, angiogenesis, intimal hyperplasia, and endothelial dysfunction.[7,29] Several organs complications have been associated with the hyper-hemolysis/endothelial dysfunction subphenotypes of SCD. These complications include stroke, PH, leg ulcer, nephropathy, and priapism,[7,8] which are all associated with high hemolytic markers (bilirubin, lactate dehydrogenase, and transaminases) and low hemoglobin.

Cardiovascular complications of SCD mimic accelerated cardiovascular aging

SCD presents with several cardiovascular complications, including cardiomegaly, heart failure, pulmonary hypertension (PH), ventricular dysfunction, myocardial infarction, and so on.[30,31] Due to chronic anemia, the heart in SCD undergoes structural changes (remodeling) to compensate for increased demand, which explains why many patients have cardiomegaly. PH, which is uncommon in young healthy (non-sickle cell) population, has been reported in 30–40% of young adults with SCD based on the finding of high tricuspid regurgitation velocity (TRV) $\geq$2.5 m/s on tissue Doppler echocardiography.[6,31] However, the prevalence of PH decreases to about 10%, on right heart catheterization.[32] The predictive value of high TRV in PH is increased by the presence of associated exercise intolerance (demonstrated using 6-min walk distance) and/or high pro brain natriuretic peptide (pro BNP).[33] High TRV has been shown in several epidemiological studies to be a major risk factor of mortality in SCD.[34–36] Causes of PH in SCD are multifactorial, and could be due to pulmonary arterial hypertension, left heart disease, lung diseases, or chronic pulmonary thromboembolism.[33] Both low levels of apolipoprotein A (APO-A) and high levels of polyubiquitin are cellular markers of aging, and have been associated with pulmonary arterial hypertension in SCD.[32]

The cardiac muscles of the left ventricles in SCD undergo eccentric hypertrophy in order to maintain stroke volume (in response to chronic anemia) with minimal increase in heart rate.[31] These adaptive changes progress and eventually lead to left ventricular dysfunction. Iron overload from chronic hemolysis and recurrent transfusions can also cause impairment of cardiac functions in SCD.[31,37] Although no evidence of atherosclerosis (which is commonly associated with aging) has been reported in SCD, the effect of endothelial dysfunction leading to intimal proliferation and vascular stenosis shows significant similarity to what is seen in atherosclerosis.[8] Taken together, the changes commonly associated with the cardiovascular system of relatively young patients with SCD mirror the age-related changes seen in the cardiovascular system and that are seen with advanced age,[38,39] thereby lending credence to the postulation of accelerated cardiovascular aging in SCD.

Musculoskeletal and bone degenerative changes of SCD are indicators of accelerated aging

SCD is associated with osteopenia, osteoporosis, and osteomyelitis.[40,41] Some of these bone changes are markers of bone aging, which predispose patients to pathological fractures.[42] A decreased activity of osteoblasts, which has been associated with increased number of aged neutrophils, is a common feature of SCD.[42] In addition, SCD increases the likelihood of osteonecrosis of the bone, which can culminate with advanced osteoarthritis of a joint.[40,41]

Sickle cell nephropathy could also aggravate bone and musculoskeletal changes through disturbed calcium and vitamin D homeostasis, and urate arthropathy (gout).[6,41] Sickle cell mice exhibit decrease speed, increased stance instability, altered walking gait and high likelihood of hesitance stop, which are associated with either pain from arthritis or neurodegenerative changes,[43] akin to what has been reported in the Klotho knockout aging mouse model.[44] Taken together, these bone complications parallel what is seen in the aged general population.[45]

Increased risk of neurological injuries and cognitive abnormalities in young persons with SCD

The incidence of stroke in the young population is generally low. However, SCD is a major risk factor for stroke in the young, including among children.[28] The cumulative incidence of stroke in SCD is about 11% by the second decade, that is, in the absence of stroke preventive intervention such as chronic blood transfusion or hydroxyurea therapy. Stroke in SCD is associated with cerebral vasculopathy, low hemoglobin, and disturbed cerebral hemodynamics as evidenced by high transcranial Doppler velocity ($\geq$200 cm/s).[28] Stroke

causes physical incapacitation, and is associated with motor, sensory, and cognitive deficits. The mortality rate is also increased in stroke. The most prevalent neurological injury associated with SCD is silent cerebral infarctions (diagnosed with at least 1.5 Tesla magnetic resonance imaging [MRI]). Silent cerebral infarcts are reported in about 53% of adults with SCD and are progressive with age.[11] In comparison, the prevalence of silent cerebral infarcts among elderly individuals in the general population is about 20%.[46] Patients with SCD, regardless of having a neurological injury or not, develop cognitive deficit.[47] However, the level of cognitive deficit is comparatively more profound in patients with neurological injury evidenced by lower full-scale intelligent quotient, lower educational attainment, and decreased chances of employability.[47–49]

Abnormalities of sphingolipids metabolism, especially increased acid sphingomyelinase, have been shown to play a role in age-related neuroinflammation and neurodegenerative changes.[50,51] Recent studies in animal models of SCD have also shown that presence of cognitive impairment in 6 months[52] and in 13 months[53] old mice have cellular evidence of neuroinflammation and neurodegeneration as observed in aged non-sickle cell mice (described earlier). Taken together, neurological injuries associated with SCD at a relatively young age suggest accelerated cerebrovascular aging.

Renal morphological and functional changes in SCD can be both a cause and effect of accelerated aging

Various morphological changes have been reported in the kidneys of patients with SCD. Glomerular hypertrophy, capillary congestions, glomerulosclerosis, and fibrosis have been documented as part of SCD-related renal changes.[54] Some of the changes like glomerulosclerosis and tubulofibrosis are ordinarily associated with aging kidney in normal individuals;[55] however, these changes are reported commonly in young individuals with SCD.[54] Kidney changes associated with SCD are progressive and start from childhood.[54] Unlike in SCD, the glomerular filtration rate starts a steady decline around the age of 40 years in individuals without SCD.[55]

The underlying mechanism of renal changes in SCD is multifactorial. The medullary area of the kidney is prone to hypoxia, acidosis, and hyperosmalarity.[54] These factors increase the rate of cellular dehydration of sickle erythrocytes, and thus predispose to sickling in the renal medulla. The blood flow in the vasa recta is also comparatively sluggish; hence, further increasing the transit time and more likelihood of sickling.[54] These conditions will lead to infarctions of the vasa recta, culminating with failure of the kidney to concentrate urine.

Nephropathy with proteinuria is a commonly reported morbidity of SCD, which accounts for 16–18% of SCD-related mortality.[54] The renal pathologies seen in SCD could cause acute or chronic kidney disease as a result of ischemia–reperfusion injury or the deleterious effect of the filtered hemoglobin. Nephropathy is generally a progressive disease, which is associated with endocrine failure (erythropoietin and 1,25-dihydroxycholecalciferol) with attendant systemic effects that resemble accelerated aging.[56,57] Inadequate secretion of erythropoietin by the kidney in response to low hemoglobin drive aggravates chronic hemolytic anemia of SCD and might even result in transfusion dependence. Uremia also reduces erythrocyte survival by damaging red cell membrane, making them prone to phagocytosis by the macrophages in the reticuloendothelial system.[58] There could also be nutritional anemia from malnutrition and dialysis-related nutrients deficiency, in addition to increased hepcidin that interferes with intestinal absorption of iron.[57]

The other important endocrine dysfunction associated with the nephropathy is abnormal vitamin D metabolism. Calcium absorption from the gastrointestinal tract is regulated by an active vitamin D called 1,25-dihydroxycholecalciferol (calcitriol), which is produced by the kidney.[56] As a result of sickle cell nephropathy, the affected patients might have features of hypocalcemia, low bone mineralization, and ultimately increased likelihood of developing renal osteodystrophy.[59] Overall, both metabolic, organ, and physical changes associated with sickle cell nephropathy shows features of accelerated aging which leads to increased risk of mortality in SCD.

Immunosenescence seems to characterize immune changes in SCD

The spleen is an important organ that serves as a filter for microbes, aged/damaged erythrocytes, and plays a role in generating IgM-producing B memory cells in response to incident infections.[60] The spleen performs these functions during the passage of blood through the white and red pulps. Often, the red pulp of the spleen becomes inundated with sieving sickle red cells, thereby failing to perform other critical immune functions.[61] The spleen is also vital in activation of the complement system through synthesis of tuftsin and properdin.[60] Importantly, the macrophages of the spleen can directly remove encapsulated organisms that have not been opsonized.

SCD is associated with early-onset hyposplenism and even functional asplenia.[60,61] Therefore, the immune system of patients with SCD shows vulnerability especially to encapsulated microbes, akin to what is seen the elderly.[62] This predisposes the patients to infections, a common cause of morbidity and mortality in SCD.[61]

Zinc deficiency has also been observed in more than 60% of patients with SCD.[61] Increased demand from high protein turnover in SCD, and failure of reabsorption at the renal tubular system due to damage, explains why zinc deficiency is common in this population. Zinc deficiency affects the immune system through stimulating increased cortisol secretion, which causes lymphopenia due to programmed B- and T-cells death in bone marrow and thymus.[63] Several studies have reported age-related decrease in zinc level in the elderly population.[63] In addition, a number of the immune changes in SCD have similarities to immunosenescence seen in the elderly, where defective phagocytosis and decreased naïve T cells are common features.[62]

Conclusions

The cellular and physical changes associated with SCD at a relatively young age parallel what has been reported in the aged non-SCD population. Major end-organ complications, disturbance of homeostasis, loss of physical function, and mortality are hallmarks of aging that are commonly seen in children and young adults with SCD. Therefore, it is imperative to extend the frontiers of research on SCD to the accelerated aging syndrome and doing so would likely pave way for newer therapeutic interventions, including strategies to improve longevity and quality of life.

AUTHORS' CONTRIBUTIONS

I.M.I. contributed to writing – original draft preparation. H.I.H., I.M.I., and E.A.B. contributed to writing – review and editing. H.I.H., I.M.I., and E.A.B. contributed to intellectual content input. H.I.H. contributed to supervision. All authors have read and agreed to the submission of this version of the manuscript.

DECLARATION OF CONFLICTING INTERESTS

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

FUNDING

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: Dr. H.I.H. is supported by grants from The National Institutes of Health (R01 HL138423, R01 HL156024, 3R01 HL138423-05S, and 1R01AG072592-01) and Dr I.M.I. is supported by a grant from the American Society of Hematology (ASH Global Research Award).

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REFERENCES

1. Mulumba LL, Wilson L. Sickle cell disease among children in Africa: an integrative literature review and global recommendations. *Int Afr Nurs Sci* 2015;**3**:56–64
2. Piel FB, Patil AP, Howes RE, Nyangiri OA, Gething PW, Williams TN, Weatherall DJ, Hay SI. Global distribution of the sickle cell gene and geographical confirmation of the malaria hypothesis. *Nat Commun* 2010;**1**:104
3. Serjeant GR. Mortality from sickle cell disease in Africa. *BMJ* 2005; **330**:432
4. Chakravorty S, Williams TN. Sickle cell disease: a neglected chronic disease of increasing global health importance. *Arch Dis Child* 2015; **100**:48–53
5. Serjeant GR, Ghosh K, Patel J. Sickle cell disease in India: a perspective. *Indian J Med Res* 2016;**143**:21–4
6. Steinberg MH. Sickle cell anemia, the first molecular disease: overview of molecular etiology, pathophysiology, and therapeutic approaches. *Sci World J* 2008;**8**:1295–324
7. Kato GJ, Steinberg MH, Gladwin MT. Intravascular hemolysis and the pathophysiology of sickle cell disease. *J Clin Invest* 2017;**127**:750–60
8. Kato GJ, Hebbel RP, Steinberg MH, Gladwin MT. Vasculopathy in sickle cell disease: biology, pathophysiology, genetics, translational medicine, and new research directions. *Am J Hematol* 2009;**84**:618–25
9. Ruan L, Zhang X, Li R. Recent insights into the cellular and molecular determinants of aging. *J Cell Sci* 2018;**131**:1–10
10. Kooman JP, Broers NJH, Usvyat L, Thijssen S, van der Sande FM, Cornelis T, Levin NW, Leunissen KM, Kotanko P. Out of control: accelerated aging in uremia. *Nephrol Dial Transplant* 2013;**28**:48–54
11. Chaturvedi S, Ghafuri DL, Jordan N, Kassim A, Rodeghier M, DeBaun MR. Clustering of end-organ disease and earlier mortality in adults with sickle cell disease: a retrospective-prospective cohort study. *Am J Hematol* 2018;**93**:1153–60
12. Robert L. Cellular and molecular mechanisms of aging and age related diseases. *Pathol Oncol Res* 2000;**6**:3-9
13. Sinclair D, Mills K, Guarente L. Aging in *Saccharomyces cerevisiae*. *Annu Rev Microbiol* 1998;**52**:533-60
14. Molano A, Huang Z, Marko MG, Azzi A, Wu D, Wang E, Kelly SL, Merrill AH Jr, Bunnell SC, Meydani SN. Age-dependent changes in the sphingolipid composition of mouse CD4+ T cell membranes and immune synapses implicate glucosylceramides in age-related T cell dysfunction. *PLoS ONE* 2012;**7**:e47650
15. Aslan M, Kirac E, Kaya S, Ozcan F, Salim O, Kupesiz OA. Decreased serum levels of sphingomyelins and ceramides in sickle cell disease patients. *Lipids* 2018;**53**:313-22
16. Aubert G, Lansdorp PM. Telomeres and aging. *Physiol Rev* 2008;**88**: 557-79
17. Altura BM, Shah NC, Shah GJ, Pérez-Abela JL, Altura BT. Magnesium deficiency results in oxidation and fragmentation of DNA, down regulation of telomerase activity, and ceramide release in cardiovascular tissues and cells: potential relationship to atherogenesis, cardiovascular diseases and aging. *Int J Diabetology Vasc Dis Res* 2016;**4**:1–5
18. Antwi-Boasiako C, Kusi-Mensah YA, Hayfron-Benjamin C, Aryee R, Dankwah GB, Kwawukume LA, Darkwa EO. Total serum magnesium levels and calcium-to-magnesium ratio in sickle cell disease. *Medicina* 2019;**55**:547–54
19. Colella MP, Santana B, Calado RT, Saad STO. Leukocyte telomere length correlates with disease severity and inflammation in sickle cell disease. *Blood* 2015;**126**:2173-73
20. Colella MP, Santana BA, Conran N, Tomazini V, Costa FF, Calado RT, Saad STO. Telomere length correlates with disease severity and inflammation in sickle cell disease. *Rev Bras Hematol Hemoter* 2017;**39**: 140-45
21. Orlowski M, Wilk S. Catalytic activities of the 20 S proteasome, a multicatalytic proteinase complex. *Arch Biochem Biophys* 2000;**383**: 1–16
22. Carrard G, Bulteau A-L, Petropoulos I, Friguet B. Impairment of proteasome structure and function in aging. *Int J Biochem Cell Biol* 2002;**34**:1461–74
23. Franco RS. The measurement and importance of red cell survival. *Am J Hematol* 2009;**84**:109–14
24. Warang P, Homma T, Pandya R, Sawant A, Shinde N, Pandey D, Fujii J, Madkaikar M, Mukherjee MB. Potential involvement of ubiquitin-proteasome system dysfunction associated with oxidative stress in the pathogenesis of sickle cell disease. *Br J Haematol* 2018;**182**:559–66
25. Berdasco M, Esteller M. Hot topics in epigenetic mechanisms of aging: 2011. *Aging Cell* 2012;**11**:181–86
26. Yasin Z, Witting S, Palascak MB, Joiner CH, Rucknagel DL, Franco RS. Phosphatidylserine externalization in sickle red blood cells: associations with cell age, density, and hemoglobin F. *Blood* 2003;**102**: 365–70
27. Bosman GJCGM. Erythrocyte aging in sickle cell disease. *Cell Mol Biol* 2004;**50**:81–6
28. Chaturvedi S, DeBaun MR. Evolution of sickle cell disease from a life-threatening disease of children to a chronic disease of adults: the last 40 years. *Am J Hematol* 2016;**91**:5–14
29. Steinberg MH, Sebastiani P. Genetic modifiers of sickle cell disease. *Am J Hematol* 2012;**87**:795–803
30. Bode-Thomas F, Hyacinth HI, Ogunkunle O, Omotoso A. Myocardial ischaemia in sickle cell anaemia: evaluation using a new scoring system. *Ann Trop Paediatr* 2011;**31**:67-74
31. Gladwin MT, Sachdev V. Cardiovascular abnormalities in sickle cell disease. *J Am Coll Cardiol* 2012;**59**:1123–33
32. Anjum F, Lazar J, Soh J, Albitar M, Gowda S, Hussain MM, Wadgaonkar R. Dysregulation of ubiquitin-proteasome pathway and

apolipoprotein a metabolism in sickle cell disease–related pulmonary arterial hypertension. *Pulm Circ* 2013;**3**:851–5
33. Gordeuk VR, Castro OL, Machado RF. Pathophysiology and treatment of pulmonary hypertension in sickle cell disease. *Blood* 2016; **127**:820–8
34. Chaturvedi S, Labib Ghafuri D, Kassim A, Rodeghier M, DeBaun MR. Elevated tricuspid regurgitant jet velocity, reduced forced expiratory volume in 1 second, and mortality in adults with sickle cell disease. *Am J Hematol* 2017;**92**:125–30
35. Klings ES, Farber HW. Pulmonary hypertension as a risk factor for death in patients with sickle cell disease. *N Engl J Med* 2004;**350**: 2521–2
36. Nouraie M, Darbari DS, Rana S, Minniti CP, Castro OL, Luchtman-Jones L, Sable C, Dham N, Kato GJ, Gladwin MT, Ensing G, Arteta M, Campbell A, Taylor JG 6th, Nekhai S, Gordeuk VR. Tricuspid regurgitation velocity and other biomarkers of mortality in children, adolescents and young adults with sickle cell disease in the United States: the PUSH study. *Am J Hematol* 2020;**95**:766–74
37. Machado RF, Anthi A, Steinberg MH, Bonds D, Sachdev V, Kato GJ, Taveira-DaSilva AM, Ballas SK, Blackwelder W, Xu X, Hunter L, Barton B, Waclawiw M, Castro O, Gladwin MT, MSH Investigators ft. N-terminal pro-brain natriuretic peptide levels and risk of death in sickle cell disease. *JAMA* 2006;**296**:310-18
38. Lakatta EG, Levy D. Arterial and cardiac aging: Major shareholders in cardiovascular disease enterprises. *Circulation* 2003;**107**:139-46
39. Mattson MP, Cutler RG. Advances in cell aging and gerontology. *Adv Cell Aging Gerontology* 2003;**12**:97-115
40. Ballas SK. Comorbidities in aging patients with sickle cell disease. *Clin Hemorheol Microcirc* 2018;**68**:129-45
41. Farook MZ, Awogbade M, Somasundaram K, Reichert ILH, Li PLS. Total hip arthroplasty in osteonecrosis secondary to sickle cell disease. *Int Orthop* 2019;**43**:293-98
42. Rana K, Pantoja K, Xiao L. Bone marrow neutrophil aging in sickle cell disease mice is associated with impaired osteoblast functions. *Biochem Biophys Rep* 2018;**16**:110-14
43. Kiven S, Wang Y, Aich A, Argueta DA, Lei J, Sagi V, Tennakoon M, Bedros SJ, Lambrecht N, Gupta K. Spatiotemporal alterations in gait in humanized transgenic sickle mice. *Front Immunol* 2020;11
44. Kuro-o M, Matsumura Y, Aizawa H, Kawaguchi H, Suga T, Utsugi T, Ohyama Y, Kurabayashi M, Kaname T, Kume E, Iwasaki H, Iida A, Shiraki-Iida T, Nishikawa S, Nagai R, Nabeshima Y-i. Mutation of the mouse Klotho gene leads to a syndrome resembling ageing. *Nature* 1997;**390**:45-51
45. Syed FA, Ng AC. The pathophysiology of the aging skeleton. *Curr Osteoporos Rep* 2010;**8**:235-40
46. Vermeer SE, Longstreth WT, Koudstaal PJ. Silent brain infarcts: a systematic review. *Lancet Neurol* 2007;**6**:611-9
47. Prussien KV, Jordan LC, DeBaun MR, Compas BE. Cognitive function in sickle cell disease across domains, cerebral infarct status, and the lifespan: a meta-analysis. *J Pediatr Psychol* 2019;**44**:948-58
48. Sanger M, Jordan L, Pruthi S, Day M, Covert B, Merriweather B, Rodeghier M, DeBaun M, Kassim A. Cognitive deficits are associated with unemployment in adults with sickle cell anemia. *J Clin Exp Neuropsychol* 2016;**38**:661-71
49. Schatz J, Brown RT, Pascual JM, Hsu L, DeBaun MR. Poor school and cognitive functioning with silent cerebral infarcts and sickle cell disease. *Neurology* 2001;**56**:1109-11
50. Alessenko AV, Albi E. Exploring sphingolipid implications in neurodegeneration. *Front Neurol* 2020;**11**:437
51. Park MH, Jin HK, Bae J-s. Potential therapeutic target for aging and age-related neurodegenerative diseases: the role of acid sphingomyelinase. *Exp Mol Medicine* 2020:1-10
52. Wang L, Almeida LE, de Souza Batista CM, Khaibullina A, Xu N, Albani S, Guth KA, Seo JS, Quezado M, Quezado ZM. Cognitive and behavior deficits in sickle cell mice are associated with profound neuropathologic changes in hippocampus and cerebellum. *Neurobiol Dis* 2016;**85**:60-72
53. Hardy RA, Rached NA, Jones JA, Archer DR, Hyacinth HI. Role of age and neuroinflammation in the mechanism of cognitive deficits in sickle cell disease. *Exp Biol Med (Maywood)* 2021;**246**:106-20
54. Nath KA, Hebbel RP. Sickle cell disease: renal manifestations and mechanisms. Nat Rev Nephrol 2015;**11**:161-71
55. Schlanger LE, Bailey JL, Sands JM. Aging and the kidney: clinical and pathophysiologic issues. In:Kimmel P, Rosenberg M (eds) Chronic renal disease. Amsterdam: Elsevier, 2020 pp.249–62
56. Al-Badr W, Martin KJ. Vitamin D and kidney disease. *Clin J Am Soc Nephro* 2008;**3**:1555-60
57. Yugavathy N, Huri HZ, Kun LS, Bin Abdul Gafor AH, Geot WM, Bavanandan S, Seng WH. Clinical and genetic markers of erythropoietin deficiency anemia in chronic kidney disease (predialysis) patients. *Biomark Med* 2020;**14**:1099-108
58. Vos FE, Schollum JB, Coulter CV, Doyle TCA, Duffull SB, Walker RJ. Red blood cell survival in long-term dialysis patients. *Am J Kidney Dis* 2011;**58**:591-98
59. Hruska KA. Renal osteodystrophy. *Baillières Clin Endocrinol Metab* 1997;**11**:165–94
60. Brousse V, Buffet P, Rees D. The spleen and sickle cell disease: the sick(led) spleen. *Br J Haematol* 2014;**166**:165-76
61. Booth C, Inusa B, Obaro SK. Infection in sickle cell disease: a review. *Int J Infect Dis* 2010;**14**:e2-e12
62. Bürkle A, Caselli G, Franceschi C, Mariani E, Sansoni P, Santoni A, Vecchio G, Witkowski JM, Caruso C. Pathophysiology of ageing, longevity and age related diseases. *Immun Ageing* 2007;**4**:4
63. Haase H, Rink L. The immune system and the impact of zinc during aging. *Immun Ageing* 2009;**6**:9