



The Gut Microbiome in Sickle Cell Disease: Pathobiology, Biomarkers and Therapeutic Opportunities in Nigerian Populations

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Abstract

Sickle cell disease (SCD) is one of the major hereditary haemoglobin diseases in people of African descent and Nigeria accounts for a large share of the worldwide burden. The molecular foundation of SCD is well understood, however there is emerging evidence that disease severity and consequences are determined by interactions between host genetics, immunology, metabolism, environmental exposures and the gut flora. The gut microbiome is a complex community of bacteria, archaea, fungi, viruses and their genes and metabolites that contribute to the intestinal barrier integrity, immunological control and metabolic balance. In SCD, repeated intestinal ischaemia, hypoxia-reperfusion damage, inflammation, haemolysis, drug exposure and dietary variables may disturb this microbial ecology, resulting in dysbiosis and increased intestinal permeability. Research in persons with SCD has shown shifts in microbial diversity and changes in taxa linked to inflammation and short-chain fatty-acid synthesis. Furthermore, experimental research shows that alterations in gut microbes may affect vaso-occlusion, immunological activation and chronic pain. In particular, increases in beneficial species such as *Akkermansia muciniphila* and butyrate-producing organisms such as *Roseburia* have been identified as possible therapeutic targets. Subsequently, microbial composition, microbial metabolites, inflammatory indicators and intestinal permeability markers may become biomarkers for disease activity and treatment response. However, information especially from Nigerian patients remains scarce, and a 2026 Nigerian-led systematic-review procedure points to the need for greater characterisation of gut microbiomes in African children and adolescents with SCD. Herein, we describe the pathobiological link between the gut microbiome and SCD, highlight possible microbiome-based biomarkers and treatment options in the setting of Nigerian people and emphasise the necessity for locally generated data.

Keywords: Sickle cell disease, Gut microbiome, Pathobiology, Biomarkers, Therapeutic opportunities.

Introduction

Sickle cell disease is an inherited haemoglobinopathy that is mostly caused by the presence of haemoglobin S due to a pathogenic mutation in the HBB gene. Under low oxygen tension, haemoglobin S polymerises and produces a hard sickle cell [1]. These cells undergo rapid haemolysis and block the microcirculation leading to anaemia, tissue ischaemia, inflammation and repeated vaso-occlusive crises (VOCs). The clinical picture of SCD is quite heterogeneous, with patients suffering from varying combinations and frequencies of discomfort, acute chest syndrome, stroke, infection, renal illness, pulmonary problems and chronic organ damage. Environmental, genetic, dietary and socioeconomic variables have a role in this variability[2].

Given the vast population size and the high incidence of the sickle haemoglobin gene in several areas, Nigeria is of particular importance in the world SCD landscape. Thus, improved knowledge of variables that affect disease manifestation has great public-health importance. The standard therapy of SCD includes preventative care, immunisation, analgesia,

transfusion, hydroxyurea and other disease modifying interventions. However, repeated pain, increasing organ damage, and chronic inflammation remain key issues. This has prompted exploration of biological systems other than the haemoglobin molecule itself[3].

The gut microbiome is one area that's growing. The gastrointestinal tract is home to a very diversified microbial population that is involved in digesting, synthesis of bioactive metabolites, immunological development, and maintenance of intestinal barrier function. Changes in the makeup or function of this community, called dysbiosis, have been connected with inflammatory and metabolic disorders. The evidence is mounting that SCD may potentially be related with abnormalities in the gut microbiota[4].

The relationship might be bidirectional. Microbial dysbiosis can enhance systemic inflammation and immunological activation. SCD-associated intestinal hypoxia, vaso-occlusion and inflammation can affect the gut environment. In a research of 14 SCD patients and 14 healthy controls, significant variations were seen in stool microbiota, such as a decreased proportion of Firmicutes to Bacteroidetes and alterations in many bacterial families. The research also reported microbiome abnormalities in a humanised SCD mouse model, thereby providing experimental evidence for the connection between SCD and gut dysbiosis[5].

Pathobiology of the Gut Microbiome in Sickle Cell Disease

Intestinal ischaemia is an important mechanism associating SCD with gut microbiota. Sickled erythrocytes can occlude the micro vascularity of the gastrointestinal tract. Repeated bouts of hypoxia and reperfusion may affect tight-junction and intestinal epithelial cell integrity. The increased intestinal permeability can allow microbial products such as lipopolysaccharide and other pathogen-associated molecular patterns to penetrate the intestinal barrier. These chemicals can activate innate immune receptors and promote systemic inflammation [6].

This pathway is particularly relevant, as inflammation is already a significant aspect of SCD pathogenesis. Haemolysis releases haemoglobin and other erythrocyte-derived compounds, which can induce oxidative stress, endothelial dysfunction and inflammatory signalling. Vascular adhesion and vaso-occlusion are mediated by activated leukocytes and endothelial cells. Furthermore, if disruption of the intestinal barrier further increases exposure to microbial products, a positive feedback loop may form where SCD linked ischaemia promotes dysbiosis and barrier damage and microbial products further enhance systemic inflammation[7].

Another relationship might be the microbial metabolites. Bacterial fermentation of food substrates produces short chain fatty acids (SCFAs), mainly acetate, propionate and butyrate. Butyrate is vital for colonocyte metabolism, intestinal barrier integrity and can affect regulatory immunological pathways. Recent microbiome studies in SCD have demonstrated decreased microbial diversity and depletion of SCFA generating species, along with alterations in microbial metabolic pathways [8].

The microbiota may affect pain, too. Chronic pain is a key source of morbidity in SCD, although the reasons are more than just episodic vascular occlusion. For experimental investigations, SCD mice and human samples are used to demonstrate that gut microbiota and microbial metabolites may impact chronic widespread pain through vagus nerve pathways. One possible key microbial change discovered was a decrease in the abundance of *Akkermansia muciniphila*. Bilirubin (a metabolite linked with haemolysis) was also involved in this gut-brain-pain relationship[9].

Akkermansia muciniphila is of special interest due to its interactions with the intestinal mucus layer and its role in maintaining the epithelial barrier function. Another organism of relevance is *Roseburia*, a genus of bacteria that produce butyrate. Reduced numbers of these organisms may affect intestinal barrier function and decrease anti-inflammatory signals. A recent study expressly recommended *A. muciniphila* and *Roseburia* as possible targets for microbiome-based treatments to SCD problems [10].

However, microbiome data should not be taken as proof for independent causality of individual bacterial species in SCD problems. Diet, age, location, antibiotics, socioeconomic situations, drugs and other host variables have a substantial impact on the gut flora. Antibiotics and analgesics for example can profoundly affect microbial makeup. Hydroxyurea may potentially influence the microbiome, and current data suggests that hydroxyurea may partially restore microbial balance, although residual dysbiosis may still exist[11].

These factors are particularly significant for Nigeria. The dietary habits, food preparation, cleanliness, exposure to infectious illness, availability of antibiotics, and access to health care are different than in North American and European communities where much of the current microbiome research has been performed. Therefore, studies of microbiota from other populations cannot be presumed to reflect Nigerian patients automatically.

The Gut Microbiome as a Source of Biomarkers

A biomarker is a quantifiable trait that might be biological in nature, and could offer information on illness state, prognosis, disease causes or response to therapy. There are multiple possible classes of SCD indicators in the gut microbiota. First is microbial composition. Differences in bacterial diversity, community structure and abundance of certain taxa may possibly differentiate persons with SCD from healthy controls or identify patients at elevated risk of problems. Studies have identified changes in microbial communities and loss of diversity or specific beneficial species. However, the taxonomic biomarkers need confirmation in large populations as microbiome makeup varies widely among individuals[12]. The second group is metabolites of microbes. SCFAs, bile-acid derivatives, tryptophan metabolites and other products of bacterial metabolism may give better useful indicators than bacterial abundance itself. This is crucial since two persons might have different bacterial species yet with comparable metabolic activities. Therefore, a metabolomic method may be able to detect biochemical markers related to VOCs, chronic pain or organ problems.

Third, microbial indicators might be incorporated with traditional inflammatory and haematological markers. C-reactive protein, interleukin-6, tumour necrosis factor- α , leukocyte counts and indicators of haemolysis may offer further information on systemic inflammation. Recent studies have also investigated correlations between gut microbial characteristics, inflammatory cytokines, and aged-like neutrophil populations in SCD[13].

Fourth, intestinal permeability per se may be a relevant indicator. Markers of epithelial barrier breakdown and bacterial translocation may identify individuals with gut damage that is important in systemic inflammation. The combined profile of stool microbiome, circulating microbial products, inflammatory markers and clinical outcomes can offer a more meaningful illness picture than any single marker[14].

This would have to be developed for Nigerian communities through locally planned longitudinal research. One of the key priorities would be to enrol patients from diverse geographical regions of Nigeria and include healthy controls matched for age, sex, diet and geography. Participants should be evaluated at steady state and during VOCs. Details on antibiotics, hydroxyurea, analgesics, transfusions, diet, and recent infections should be obtained. Importantly, a Nigerian-led protocol published in 2026 reveals increased interest in rigorously evaluating gut microbiota profiles across children and adolescents with SCD and expressly calls out pharmaceutical and environmental impacts as relevant research concerns.

Therapeutic Possibilities

Targeted microbiome therapy might be a viable addition, not a substitute, to current SCD therapy. One potential method is food change. Diet is amongst the greatest drivers of gut bacteria composition and fermentable fibre rich diets can stimulate the synthesis of SCFAs. Nigerian eating habits offer chances for contextually relevant treatments employing inexpensive sources of nutritional fibre, legumes, vegetables, fruits and whole grains. However, such treatments must be thoroughly examined and not just assume that a traditional cuisine is inevitably good for the microbiota.

Another approach is to utilise probiotics. Probiotics using certain strains of *Lactobacillus*, *Bifidobacterium* or other organisms can enhance the microbial balance and intestinal barrier function. Evidence supporting the use of probiotics particularly to avoid problems of SCD is still lacking. Probiotic effects are strain specific and therapies that are helpful in one group may not have the same benefits in another.

Third possibility is prebiotics or synbiotics treatment. Prebiotics are defined as substrates that preferentially promote the growth of beneficial bacteria. Synbiotics are a combination of prebiotics and probiotics. Instead of adding particular bacterial strains, these techniques might boost SCFA synthesis and recover microbial functions[15]. A fourth technique is by direct supplementation with microbial metabolites. Butyrate is of special importance as it protects the health of intestinal epithelial cells and has immunomodulatory effects. There is additional evidence that butyrate-related pathways may alter foetal haemoglobin expression, offering a potential mechanistic connection between microbial metabolism and the core biology of SCD.

Another potential approach is faecal microbiota transplantation (FMT), although its use in SCD remains experimental. FMT means transferring a microbial community from a vetted donor to a recipient. While the notion of restoring the microbiome is intriguing, the potential for transmission of pathogenic organisms and uncertain long-term effects of the microbiome suggest that FMT should not be viewed as a standard treatment for SCD outside of well controlled studies at the present time[16].

For Nigeria, therapeutic development should focus on safety, cost and scalability. Interventions that are not readily available may be done using pricey imported microbial products. Therefore, research into locally accessible prebiotic foods, defined microbial strains and standardised metabolite-based therapies should be particularly beneficial. This type of study should be done in conjunction with traditional SCD therapy, not as a stand-alone approach[17].

The microbiome may potentially hold out the prospect of personalised medicine. Biologically, people with SCD are varied, and not all patients with dysbiosis will have the same microbial profile. In the future stool metagenomics and metagenomics may be used to identify patients with depletion of certain functional pathways and hence select individualised dietary, probiotic or metabolite-based therapies. However, there is currently no data to regularly recommend such personalised microbiome therapy, while the concept is an interesting field for research[18].

Conclusion

The gut microbiota is a developing feature of SCD biology. Evidence from the existing literature supports the association of SCD with intestinal dysbiosis, altered microbial diversity, alterations in SCFA generating organisms and disturbance of intestinal barrier function. Such alterations may lead to inflammation, vaso-occlusion and chronic pain via interplay between intestinal permeability, microbial products, immunological activation, metabolism and the gut-brain axis. "There is potential for important clinical uses." Microbial taxa, microbial metabolites, intestinal permeability indicators and integrated microbiome-inflammatory signatures may ultimately be used as biomarkers for disease activity, complications and treatment response. Other viable supplementary treatments include food modification, probiotics, prebiotics, synbiotics, microbial metabolites and microbiota-based medicines that have been extensively studied. However, the evidence base is still evolving and much of the research available has been done outside Nigeria. Therefore, Nigerian-specific microbiome investigations are important. Differences in food, exposure to antimicrobials, infectious illnesses, location, genetics and health care settings may cause microbiome patterns different to those documented elsewhere. Multicentre Nigerian cohorts, harmonised techniques for stool sample and sequencing, longitudinal clinical follow-up, metagenomic and metabolomic analysis, and combination with traditional biomarkers of SCD will further increase the evidentiary basis. Ultimately, knowledge of the gut microbiome in Nigerian patients with SCD might contribute to a more complete model of illness in which haemoglobin biology, vascular dysfunction, immunology, nutrition and microbial ecology are evaluated together. Such knowledge may provide avenues for economical, culturally relevant and personalised supplementary therapy, while enhancing understanding of the biochemical mechanisms shaping SCD outcomes in African communities.

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