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A Review of Advancements in Laboratory Diagnostics For Sickle Cell Disease

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ABSTRACT

Sickle Cell Disease (SCD) is a global health concern that significantly impacts morbidity, mortality, and quality of life. Early detection and comprehensive care have been shown to improve outcomes, but access to accurate and cost-effective diagnostic tools remains a challenge, particularly in low- and middle-income countries. Traditional laboratory methods, such as electrophoresis, isoelectric focusing, high-performance liquid chromatography, and DNA identification techniques, are highly accurate but often inaccessible due to high costs, resource limitations, and logistical barriers. This review examines the advantages and limitations of current SCD diagnostic techniques and explores recent advancements in point-of-care testing (POCT) that aim to improve access to screening and diagnosis. Emerging POCT methods, including lateral flow strips, paper-based tests, smartphone-based diagnostics, aqueous multiphase systems, HemeChip, microfluidic paper-based devices, shear gradient microfluidic adhesion systems, electrical impedance microflow cytometry, and spatio-temporal cell dynamics analysis, offer promising alternatives for resource-limited settings. However, these techniques must address challenges related to sensitivity, specificity, cost, portability, and training requirements. The integration of innovative POCT technologies with traditional laboratory methods has the potential to enhance early detection and treatment of

SCD, ultimately reducing the global burden of the disease. Collaborative efforts between global health organizations, governments, and research institutions are crucial for developing, scaling, and implementing accessible diagnostic solutions for SCD in underserved populations.

KEYWORDS: Sickle Cell Disease, SCD, Laboratory Diagnosis.

1. Introduction

Sickle Cell Disease (SCD) is an autosomal recessive inherited disorder that affects hemoglobin in human red blood cells (RBCs) (Gardner, 2018). RBCs are the most abundant cellular component of whole blood (Abdulraheem Fadhel et al., 2017), and their primary role is to transport oxygen throughout the body. SCD is caused by a point mutation in the beta-globin gene of hemoglobin, where a hydrophilic glutamic acid residue is replaced by a hydrophobic valine residue at the sixth position of the amino acid sequence (Glu6Val or E6V mutation). This mutation transforms normal hemoglobin into hemoglobin S (HbS) (Gardner, 2018). Under hypoxic conditions, RBCs containing HbS undergo morphological and functional alterations (Ingram, 1958). Hemoglobin S polymerizes into long fibers when deoxygenated, distorting the cell and giving it the characteristic sickle shape (Hahn & Gillespie, 1927). Other hypoxic conditions can also induce changes in RBC morphology and function; however, their symptoms are distinct from those of SCD. For instance, a relationship exists between leukemia, RBC count and morphology, and fever (Viana, 2011). Leukemia, a cancer type, leads to the production of abnormal RBCs and white blood cells, impairing the body's proper functioning. Deformed erythrocytes lose their oxygen-carrying efficiency, contributing to hypoxia and blood acidosis. To compensate for hypoxia, the body increases blood cell volume. However, leukemia can be differentiated from SCD by distinct signs and symptoms such as abnormal weight loss, lymph node swelling, hepatomegaly, splenomegaly, bruising (ecchymosis), recurrent nosebleeds (epistaxis), hematomas, and bone pain or tenderness. Thus, while hypoxia can induce acidosis, its manifestations differ significantly between conditions (Fievet et al., 1987). Severe hypoxia triggers a rapid increase in RBC volume, and in dehydration, RBC concentration increases despite no change in the absolute number of cells (Dill & Costill, 1974).

Sickle cell disease (SCD) poses significant health risks, including increased morbidity and mortality, multi-system disorders, recurrent hospitalizations, acute painful episodes, and life-threatening complications such as invasive bacterial infections (e.g., pneumococcal infections), acute chest syndrome, progressive multi-organ damage, chronic hemolysis, severe anemia, and stroke. Individuals with SCD experience markedly poor quality of life despite advancements in management strategies (Nikhar 2011). Early and timely screening or diagnosis, followed by the implementation of a comprehensive care package (including simple and effective interventions such as penicillin prophylaxis, immunizations, blood transfusions, and hydroxyurea), has been shown to enhance the quality of life for individuals with SCD (Lee et al., 1995; Nikhar et al., 2011). Nevertheless, there are substantial challenges in ensuring equitable access to screening and diagnostic services for SCD, particularly in low- and middle-income countries (Benson & Therrell, 2010; Knight-

Madden et al., 2019).

Effective screening programs require well-established specialized diagnostic facilities, trained personnel, and efficient systems for specimen collection, storage, transportation, diagnosis, follow-up, and management (Grosse et al., 2011; McGann & Hoppe, 2017). Although diagnostic tools such as agarose gel electrophoresis, high-performance liquid chromatography (HPLC), isoelectric focusing (IEF), capillary zone electrophoresis (CZE), and DNA identification techniques are highly accurate, they are costly and often inaccessible in resource-constrained settings or emergency situations (McGann & Hoppe, 2017; Rees et al., 2010).

Countries such as the United States, the United Kingdom, and Brazil, which have implemented universal newborn screening programs (Streetly et al., 2008; Weil et al., 2020), report significant improvements in the number of children with SCD receiving comprehensive care, including effective preventive measures and increased life expectancy. However, many low- and middle-income countries, such as Angola, Ghana, and Uganda, have only piloted screening programs and have not achieved full implementation due to limited financial resources, laboratory capacity, technical supplies, and follow-up systems (Benson & Therrell, 2010; Knight-Madden et al., 2019).

Both the World Health Organization (WHO) and the National Institutes of Health (NIH) advocate for the development of point-of-care testing (POCT) to improve access to diagnostic services and facilitate prompt management of various conditions, including SCD. POCT aims to ensure the availability of safe and effective diagnostics to individuals who face barriers to accessing traditional testing methods, such as those in remote locations or emergency situations. POCT is expected to enhance access to screening and diagnosis, thereby increasing the availability of life-saving and cost-effective interventions for individuals with SCD (Gaston et al., 1986; McGann & Hoppe, 2017).

In recent years, several innovative POCT techniques have been developed and evaluated to screen for SCD, particularly in resource-limited settings where the prevalence of SCD is high (Alapan et al., 2016; Bond et al., 2017; A. A. Kumar et al., 2014).

There are two primary forms of SCD based on the number of affected genes inherited through the mutation. The most severe and common form, sickle cell anemia (SCA), results from the homozygous inheritance of the HbS allele from both parents (Torabian et al., 2017). Individuals with SCA experience the most severe symptoms of SCD. In contrast, the heterozygous form, known as sickle cell trait (SCT), arises when one parent contributes an HbS allele while the other contributes an HbA allele (HbAS genotype). In SCT, both HbA and HbS are produced, and the condition generally does not require medical intervention. Under hypoxic conditions, HbS polymerizes, forming fibers that distort RBC shape. These distorted RBCs have a much shorter lifespan of 10–20 days compared to the normal lifespan of 120 days (Bartolucci et al., 2012). These cells are less flexible, prone to bursting while traveling through blood vessels, and not replenished quickly enough by the bone marrow. This results in hemolytic anemia (Knowlton et al., 2015). Furthermore, the

rigidity of affected RBCs causes vascular blockages, leading to complications such as severe anemia, chronic pain episodes, acute chest syndrome, organ damage, stroke, increased susceptibility to infections, and other severe conditions. In a normal oxygen environment, sickled RBCs regain their shape but may sustain irreversible damage. Currently, the only curative treatments for SCD are stem cell therapy and bone marrow transplantation. Most treatments focus on managing symptoms and complications. The U.S. Food and Drug Administration (FDA) has approved hydroxyurea as the sole medication for SCD treatment (Hosseini et al., 2016). Hydroxyurea increases fetal hemoglobin (HbF) levels, which reduces HbS concentrations, delays HbS polymerization under hypoxia, decreases RBC sickling, and mitigates associated complications. Additionally, it improves antioxidant activity, reduces cell adhesion, enhances filterability, and increases RBC count, thereby alleviating symptoms.

The World Health Organization (WHO) recognized SCD as a global public health issue in 2006 (Knowlton et al., 2015). Approximately 25% of people in Central and West Africa are affected by SCD, with 70,000–100,000 individuals impacted in the United States. Nearly all children born in developed countries, including the U.S., undergo universal newborn screening programs designed to detect diseases like SCD that require early intervention to ensure healthy development. However, in low-resource regions, such as sub-Saharan Africa, where 80% of SCD cases occur, universal screening is often infeasible due to cost and limited resources. The median lifespan of individuals with SCA is 40–50 years. In Africa, around 700 children are born daily with SCD (Yang et al., 2013). There is a critical need to assess the effectiveness of hydroxyurea treatment and develop a point-of-care (POC) home-based diagnostic device to monitor the disease frequently. Such a device would enable optimized drug dosage adjustments based on individual needs. Without timely diagnosis and early treatment, 50–90% of affected children in these regions die before age five (Makani et al., 2011; Modell & Darlison, 2008). By contrast, most children diagnosed and treated early in life survive into adulthood. Currently, SCD diagnosis relies on hemoglobin analysis techniques such as capillary electrophoresis, ion-exchange high-performance liquid chromatography, and isoelectric focusing. However, these methods require specialized equipment, making them impractical in resource-limited settings. Therefore, alternative and cost-effective diagnostic methods are urgently needed. This review examines current SCD diagnostic techniques, discussing their advantages and limitations while proposing future directions to address these challenges.

Current Laboratory Tests, Advantages, and Limitations

Early detection of Sickle Cell Disease (SCD) through newborn testing, monitoring, and therapeutic interventions can significantly reduce mortality associated with the condition. However, no single diagnostic method is universally preferred for SCD diagnosis (Smith & Kinney, 1997). The Agency for Health Care Policy and Research (AHCPR) recommends employing a combination of three techniques for newborn screening: hemoglobin electrophoresis, isoelectric focusing (IEF), and high-performance liquid chromatography (HPLC) (Ashley-Koch et al., 2000). These methods are highly reliable, effective, and demonstrate high specificity and sensitivity.

Electrophoresis is often the initial diagnostic step for SCD, separating different hemoglobin types (HbA, HbF, HbS, and HbC) based on their electrical charge (Yawson et al., 1970). This technique is suitable for both liquid and dried blood samples and commonly employs cellulose acetate membranes. The use of cellulose acetate offers advantages such as superior resolving power and reduced protein absorption (R. Kumar & Derbigny, 2019). This results in sharp protein bands with minimal trailing effects. Compared to filter paper, moist cellulose acetate membranes exhibit lower conductivity under identical conditions, minimizing heat production from the Joule effect and allowing operation at higher voltages. Although evaporation can be a concern, it can be mitigated by incorporating vapor pressure depressants such as glycol or glycerol (5–10%) in the buffer. This method is an effective option for hemoglobin measurement. Another electrophoresis technique involves citrate agar gel, which separates hemoglobin based on its charge and interaction with the agar gel. Under an electric charge at an alkaline pH, HbF migrates between HbA and HbS on cellulose acetate. This technique is semi-quantitative, straightforward to operate, and can process up to 200 samples within an hour, but it requires a densitometer for quantitation. While the densitometer enhances sensitivity, its cost of $2500 limits its feasibility in many regions.

Isoelectric focusing (IEF) separates hemoglobin variants by their net charge within a pH gradient on a gel medium. Hemoglobin molecules migrate across the gradient until reaching their isoelectric point, forming distinct and easily recognizable bands (Basset et al., 1978; Righetti, 2000). This technique offers better resolution of HbS compared to other hemoglobin forms and does not require blotting (Reddy & Franciosi, 1994). IEF provides sharper peaks in densitograms than traditional electrophoresis. However, its drawbacks include high operational costs and the need for skilled laboratory personnel.

High-performance liquid chromatography (HPLC) is another diagnostic method for detecting hemoglobinopathies (Colah et al., 2007). The preferred variant, cation-exchange HPLC (CE-HPLC), quantifies hemoglobin types based on their net charge at a specific pH (Ryan et al., 2010; Wild & Stephens, 1997). This technique involves using a negatively charged resin (stationary phase) and a positively charged solution (mobile phase) with increasing concentrations. The mobile phase competes with hemoglobin for adsorption sites, eluting hemoglobin from the stationary phase. The elution rate depends on the hemoglobin's affinity for the column. The method produces distinct peaks corresponding to different hemoglobin types, which are measured with precision. When combined with IEF, HPLC achieves a specificity and sensitivity of 99% for SCD diagnosis. Despite its accuracy and ability to automate quantification, HPLC is expensive and technically demanding.

Over the past two decades, automated capillary electrophoresis has emerged as a preferred method for analyzing abnormal hemoglobin variants in newborns and adults (Cotton et al., 2013). This method has largely replaced gel electrophoresis, IEF, and HPLC for screening. Automated systems prepare hemolysates from RBCs, and hemoglobin fractions are separated and detected rapidly using a 7.8 kV voltage, achieving a throughput of 48 samples per hour.

While these laboratory methods are accurate and sensitive, they have notable limitations. They only provide mean values for laboratory parameters and are often too complex, time-intensive, bulky, or expensive for implementation in resource-limited settings. Additionally, these methods require trained personnel for both technical operation and result interpretation.

Point-of-Care-Based Devices

Point-of-care (POC) devices are critical for the cost-effective and accurate diagnosis of SCD in resource-limited settings, where the disease prevalence is high. These devices hold the potential to revolutionize SCD diagnosis and management by offering portable, affordable solutions that require minimal training to operate and interpret. Several recent advancements in this field are discussed below.

Lateral Flow Strips

Lateral flow strips are a diagnostic tool used to identify individuals with sickle cell anemia (SCA) and sickle cell trait (SCT) (Bond et al., 2017). These strips differentiate individuals with SCA (HbSS genotype) in approximately 15 minutes using undiluted blood samples. The strips are prepared using hemoglobin extracted from donor blood, specifically HbSS and HbAA. The control line is created with rabbit anti-mouse IgG. A small blood sample (0.5–3 µL) is mixed with antibody-coated blue latex beads in a tube and then applied to the strip. The beads are conjugated with mouse anti-HbA or mouse anti-HbS antibodies. The strip is placed in a well containing running buffer and allowed to develop for 10 minutes. The results indicate the presence of SCD, SCT, or the absence of both conditions. In normal blood, only HbA binds to anti-HbA sites on the latex beads, producing a control line. In SCT, both HbA and HbS bind to their respective antibodies, producing two lines on the strip. In SCA, HbS binds to anti-HbS antibodies, producing the control and S lines. These tests are cost-effective, user-friendly, and time-efficient (St John & Price, 2014). They do not require specialized instruments or skilled personnel, making them suitable for low-resource regions. Their portability also facilitates widespread distribution.

However, lateral flow strips have certain limitations. Their fabrication process is relatively complex, and they rely on proprietary antibodies, which can increase per-test costs. Additionally, these antibodies may require specific storage conditions to prevent degradation, making the strips vulnerable to temperature fluctuations during shipping and use.

Paper-Based Test for Screening Newborns

Traditional methods for screening newborns for Sickle Cell Disease (SCD) are costly and time-intensive (Piety et al., 2017). An alternative approach involves paper-based screening using blood samples obtained from infants, providing a novel diagnostic avenue. In this method, a heel-stick is used to collect whole blood from the patient. A syringeless filter is employed to remove debris from the blood sample. Subsequently, a drop of filtered blood is deposited onto chromatography paper and left to dry for 25 minutes. The results are then analyzed, completing the screening process within approximately 40 minutes.

Paper-based screening offers a more economical solution compared to conventional SCD diagnostic methods, enabling the screening of a larger number of infants. This approach is also quicker and more portable than other diagnostic techniques, facilitating the mass production and distribution of kits globally. Nevertheless, paper-based methods are limited to detecting SCD and are unable to identify sickle cell trait (SCT) in newborns. Additionally, the technique is prone to a high rate of false-positive results due to filter malfunctions.

Sickle Cell Detection Using a Smartphone

Smartphone-based assays represent a cutting-edge method for diagnosing SCD, leveraging advancements in mobile technology (Knowlton et al., 2015). This technique uses a 3D-printed attachment incorporating optical lenses, a light-emitting diode (LED), and magnets to detect red blood cells (RBCs) affected by SCD. A blood sample is mixed with 10 mM sodium metabisulfite dissolved in a paramagnetic gadolinium solution and loaded into a microcapillary tube. This tube is inserted between magnets, and the RBCs are separated based on the density of hemoglobin types within the cells. Under deoxygenated conditions, sickle hemoglobin has a higher density.

Magnetic levitation produces distinct patterns that differ from control RBCs, which are captured in images after 15 minutes. These images are analyzed using a dedicated Android application. This approach is cost-effective and offers the potential for self-diagnosis, reducing the need for laboratory visits. Compared to traditional laboratory diagnostics, the average cost of examinations using a smartphone-based attachment is significantly lower. The portable nature of the attachment device allows individuals to perform self-diagnosis conveniently. However, smartphone-based methods cannot detect SCT, and further research is required to validate the accuracy of this technique. Additionally, the setup involving the smartphone attachment may not be user-friendly, particularly for consumers unfamiliar with the self-diagnostic process.

Aqueous Multiphase Systems (AMPS) and Multi-Phase Analyzer (MPANA) Diagnostic Techniques

Aqueous Multiphase Systems (AMPS) offer an innovative and effective method for diagnosing SCD (A. A. Kumar et al., 2014). In SCD, RBCs are abnormally shaped and can obstruct normal blood flow, leading to severe symptoms and potentially fatal outcomes. A hallmark characteristic of SCD is the high density of affected RBCs (Bartolucci et al., 2012). The AMPS technique identifies these dense RBCs by separating blood cells based on density using a microhematocrit centrifuge. This process visually differentiates individuals with SCD from those with normal hemoglobin or SCT.

AMPS is a cost-effective method, with the total cost of reagents and materials required for processing ~5 µL of blood being approximately $0.50. The diagnostic process is rapid, requiring around 10 minutes. However, the use of an expensive centrifuge limits the suitability of AMPS for home-based point-of-care (POC) settings and resource-constrained regions.

The Multi-Phase Analyzer (MPANA) is an advanced variant of AMPS. In this method, a drop of blood is introduced into a tube containing an aqueous multiphase system that forms immiscible, self-assembling step gradients (Chunda-Liyoka et al., 2018). The tube is centrifuged for 15 minutes, and blood cells are separated by density under centrifugal force. Due to their higher density, SCD-affected cells form a red spot of deformed cells at the bottom of the tube, which is easily visible to the naked eye and can be assessed by a trained technician.

Although MPANA is an innovative approach to SCD detection, it requires skilled personnel for interpretation. Additionally, the centrifugation process, which is powered by an automobile battery, reduces its portability. While the per-test cost is approximately $0.50, the expense of the centrifugation system renders this method less practical for widespread use, particularly in low-resource settings (A. A. Kumar et al., 2014).

HemeChip

The HemeChip offers a cost-effective and portable solution for diagnosing SCD and SCT (Hasan et al., 2017). This innovative device facilitates rapid and accurate detection through a three-step process. Initially, blood obtained via a finger prick is mixed with deionized water. Next, less than 1 µL of hemolysate is blotted onto a paper strip located inside the HemeChip. Finally, an electric field is applied using internal electrodes, prompting hemoglobin to migrate differentially on the cellulose paper strip. Distinct bands form due to charge separation, enabling the identification of various hemoglobin types, including HbA, S, F, and C/A2.

The diagnostic process requires trained personnel to handle the blood sample and operate the device. The results, analyzed through custom software, provide detailed information about the blood sample, allowing for a precise diagnosis of SCD or SCT. Each test costs approximately $2, and results are available within 10 minutes.

Despite its portability and cost-effectiveness as a point-of-care diagnostic platform, the HemeChip device demands a portable system comprising a rechargeable power source, a data acquisition unit, and an embedded imaging mechanism. These requirements limit its practicality in some contexts.

Microfluidic Paper-Based Devices (µPADs)

Microfluidic paper-based devices (µPADs) provide a point-of-care diagnostic method for distinguishing SCD and SCT carriers from healthy individuals, utilizing the polymerization of RBCs in whole blood (Yang et al., 2013). This technique relies on analyzing the blood stain patterns on paper to determine hemoglobin content. A blood drop mixed with phosphate buffer and a reducing agent is placed on a paper substrate, where the resulting stain indicates hemoglobin types.

If HbS is present, it interacts with the paper fibers, forming a distinct pattern of colors visible to the naked eye without requiring image analysis. This paper-fluidic approach is less expensive than other diagnostic platforms, as it avoids the need for enzymes or chemicals to induce color changes. The natural color of hemoglobin is sufficient for detection. The entire process takes approximately 20 minutes.

However, µPADs exhibit variability in specificity and sensitivity, and proper

functionality depends on maintaining ambient temperature and environmental conditions during shipping and storage.

Shear Gradient Microfluidic Adhesion (SIGMA) System

The SIGMA system utilizes a microfluidic platform functionalized with fibronectin proteins to assess RBC flow rates (Kucukal et al., 2018). This technique investigates shear-dependent adhesion using microchannels coated with vascular endothelial proteins. A single pump drives a continuous shear gradient flow at a constant rate.

HbSS RBCs display heterogeneous adhesive responses under a shear gradient when interacting with proteins such as Laminin (LN) or Fibronectin (FN). Phase-contrast imaging captures and analyzes the adhesion of RBCs to microchannel surfaces. This heterogeneity correlates clinically with inflammatory markers and iron overload in individuals with SCD. If untreated, iron overload resulting from SCD can exacerbate health risks. This system provides insights that may aid in reducing disease-associated complications.

Electrical Impedance Microflow Cytometry

Electrical impedance microflow cytometry offers a more complex but highly precise approach to diagnosing SCD (Liu et al., 2018). This technique uses a label-free flow cytometry method for non-invasive single-cell measurement under controlled oxygen conditions, combining microfluidics with electrical impedance spectroscopy.

The method identifies differences in the electrical impedance of RBCs from healthy individuals and those affected by SCD. Under hypoxic conditions, the phase of HbS molecules transitions from a soluble state to rigid fibers, altering electrical impedance. By comparing signals, SCD can be diagnosed.

However, this approach does not currently establish a relationship between disease severity and electrical impedance. Additionally, its ability to distinguish between SCT and SCD remains uncertain.

Spatio-Temporal Cell Dynamics Analysis

Spatio-temporal analysis differentiates sickle cells from healthy RBCs by analyzing cell membrane fluctuations and morphology (Javidi et al., 2018). This technique captures video holograms of cells using a digital holographic microscope. Each hologram is reconstructed into data cubes, and optical flow algorithms estimate motion fields between reconstructions.

Machine learning software processes this data to identify and diagnose sickle cells. Compared to basic laboratory diagnostics, this method offers advantages in cost, time, and accessibility. It does not require specialized personnel to operate. However, the setup's cost is elevated due to the use of expensive CMOS/CCD imaging sensors.

2. Conclusion

Sickle Cell Disease (SCD) represents a significant public health challenge, marked by severe complications, high morbidity and mortality rates, and poor quality of life

for affected individuals. Although laboratory-based diagnostic techniques such as electrophoresis, isoelectric focusing, high-performance liquid chromatography, and DNA identification methods are accurate and effective, their implementation is hindered by high costs, resource limitations, and logistical challenges in low- and middle-income countries. Universal newborn screening programs in high-income nations have demonstrated the potential to improve outcomes through early detection and comprehensive care, highlighting the need for equitable access to diagnostic and management tools.

Emerging point-of-care technologies, including HemeChip, smartphone-based diagnostics, microfluidic paper-based devices, and aqueous multiphase systems, offer promising alternatives for SCD diagnosis in resource-constrained settings. However, these methods must address challenges such as sensitivity, specificity, cost, portability, and training requirements. The integration of innovative technologies with traditional laboratory methods holds the potential to improve early detection and treatment, ultimately reducing the burden of SCD worldwide. Moving forward, collaborative efforts between global health organizations, governments, and research institutions are essential to develop, scale, and implement accessible diagnostic solutions for SCD in underserved populations.

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