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Malaria and Its Impact on Glucose Levels

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Abstract

Malaria is a significant global health issue, particularly in tropical and subtropical regions. The disease, caused by Plasmodium parasites and transmitted via female Anopheles mosquitoes, leads to severe complications including alterations in glucose metabolism. This review examines the bidirectional relationship between malaria and glucose levels, highlighting how Plasmodium infection can induce hypoglycemia due to increased glucose consumption by the parasite, and, in severe cases, cause hyperglycemia through stress responses and insulin resistance. Furthermore, individuals with pre-existing diabetes are at higher risk of complications such as ketoacidosis and hyperosmolar hyperglycemic states during malaria infections. Understanding the influence of glucose metabolism on malaria pathogenesis and patient outcomes can improve treatment strategies, particularly for managing severe cases. Regular monitoring of glucose levels is essential for reducing mortality, especially in vulnerable groups such as children and pregnant women. Identifying glucose-related biomarkers for complications may help enhance malaria prognosis and management.

Keywords: *Hyperglycaemia, hypoglycaemia, mosquito, plasmodium falciparum*

Introduction

Malaria is a severe disease caused by Plasmodium parasites, transmitted to humans by infected female Anopheles mosquitoes. It remains a leading cause of mortality globally, particularly in Africa and parts of Asia, where it is most common. Malaria can also occur in developed countries through imported cases from endemic regions. Early diagnosis and prompt treatment are critical to preventing severe outcomes [1]. Globally, malaria's mortality rate ranges from 0.3% to 2.2%, with higher rates of 11% to 30% in tropical regions where severe forms of the disease are more common [2].

The causative agent of malaria, Plasmodium, is a small protozoon with several subspecies, some of which infect humans [2][3]. Plasmodium species are intracellular parasites that accumulate malaria pigment and can be found in red blood cells or tissue. The Plasmodium life cycle is complex, involving both sexual and asexual phases that occur in mosquitoes and humans, respectively. The sexual phase takes place in the mosquito vector, while the asexual phase occurs in the human host [4][5].

Glucose is crucial for the human body, primarily regulated by insulin, a hormone produced by the pancreas. When blood glucose levels rise, the pancreas releases insulin to signal cells to absorb glucose for energy, maintaining healthy glucose levels. Conversely, when glucose levels drop, the pancreas releases glucagon, prompting the liver to release stored glucose into the bloodstream, ensuring a steady energy supply [6].

If the body cannot produce enough insulin or use it effectively, it can lead to diabetes, where high blood glucose levels cause damage to cells and organs, leading to serious health issues such as heart disease, nerve damage, and blindness. Glucose is vital for metabolism, serving as the primary energy source for cells, particularly during cellular respiration, where glucose is converted into ATP (adenosine triphosphate) to power cellular functions [7].

The brain, despite being only 2% of body weight, consumes up to 20% of the body's energy, relying heavily on glucose for proper function. Without sufficient glucose, brain function can deteriorate. Glucose also plays a key role during physical activity, meeting the increased energy demands of the body. Hormones like insulin and glucagon carefully regulate blood glucose levels, and maintaining this balance is crucial for overall health. Elevated glucose levels can lead to diabetes, which significantly increases the risk of complications like heart disease and blindness [8][9].

History of Malaria

The term "malaria" comes from the Italian words "mal'aria," meaning "bad air," due to the disease's early association with marshy areas. In the late 19th century, Charles Louis Alphonse Laveran, a French army surgeon, identified parasites in the blood of a malaria patient. Later, Dr. Ronald Ross, a British medical officer in India, discovered that mosquitoes transmitted malaria. Italian professor Giovanni Battista Grassi further demonstrated that human malaria could only be transmitted by Anopheles mosquitoes [10][11]

The Parasites

Malaria is transmitted through the bite of an infected female Anopheles mosquito. The disease is caused by eukaryotic single-celled microorganisms of the genus *Plasmodium*. Over 100 *Plasmodium* species can infect various animals, but only four infect humans: *Plasmodium falciparum*, *P. vivax*, *P. ovale*, and *P. malariae*. These species differ in morphology, immunology, geographical distribution, relapse patterns, and drug responses. *P. falciparum* is the most dangerous, responsible for severe and often fatal malaria, especially in young children in Africa [10].

Life Cycle of Malaria

The malaria parasite's life cycle is complex, requiring specialized proteins for survival in both mosquito and human hosts. Once a mosquito injects *P. falciparum* or *P. malariae* sporozoites into a human [12], they quickly travel to the liver, where they invade hepatocytes and undergo asexual replication (exo-erythrocytic schizogony). *P. ovale* and *P. vivax* sporozoites may either undergo immediate schizogony or enter a dormant stage called hypnozoite before reactivation. In the liver, each sporozoite produces tens of thousands of merozoites, which then invade red blood cells (RBCs). [13]

Inside RBCs, the parasites grow and develop through different stages, beginning with the ring-form trophozoite. The parasite metabolizes large amounts of glucose and digests hemoglobin, leading to the formation of hemozoin, a malaria pigment. The trophozoite undergoes multiple rounds of nuclear division without cytokinesis, forming schizonts that eventually release merozoites to infect more RBCs. This cycle of invasion, multiplication, and release continues, correlating with fever spikes during malaria [14]

Some merozoites differentiate into gametocytes, which are ingested by mosquitoes during a blood meal. In the mosquito's midgut, the gametocytes form gametes, which fuse to create a zygote. The zygote develops into an ookinete that penetrates the midgut wall and forms an oocyst. Sporogony occurs within the oocyst, producing many sporozoites that migrate to the mosquito's salivary glands, ready to infect a new host. The mosquito remains infective for 1–2 months, perpetuating the cycle when it bites another human.

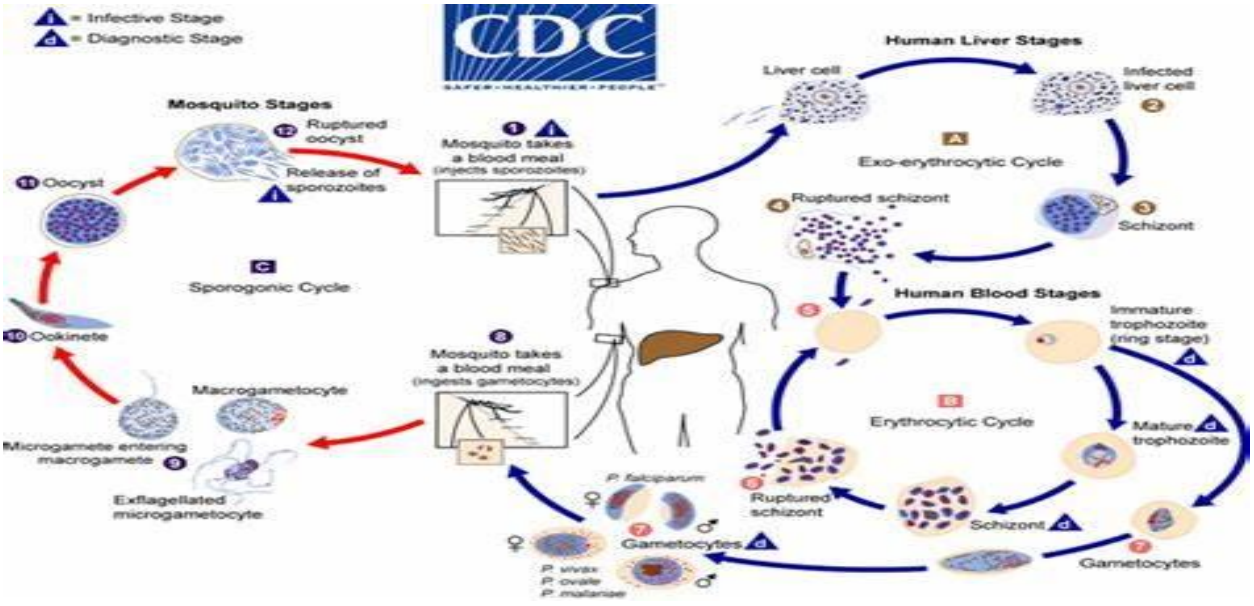

Fig. 1. *Life cycle of malaria extracted from CDC* [15]

Symptoms

Infection with *Plasmodium falciparum* is characterized by the sequestration of parasite-infected red blood cells (RBCs) in various organs, including the heart, brain, lungs, kidneys, subcutaneous tissues, and placenta. Common symptoms include fever, shivering, cough, respiratory distress, joint pain, headache, diarrhea, vomiting, and convulsions. Severe cases may lead to jaundice, kidney failure, and severe anemia, contributing to potentially fatal outcomes. While most cases of malaria do not lead to life-threatening complications, the triggers for progression from uncomplicated to severe malaria remain poorly understood. Malaria is particularly dangerous for pregnant women and young children, significantly affecting perinatal mortality. During pregnancy, *P. falciparum* infection can lead to severe complications, such as premature delivery, low birth weight, and increased infant mortality due to parasite sequestration in the placenta [16][17]

Diagnosis

Malaria diagnosis combines clinical observation, patient history, and diagnostic tests, primarily involving microscopic examination of blood. Blood samples, ideally collected when the patient's temperature is rising, are analyzed using thick blood films, allowing detection of even low parasite counts (as few as one parasite per 200 μL of blood). Rapid diagnostic tests (RDTs), or "dipstick" tests, are also used, providing results in minutes from a finger-prick blood sample. Although these tests are user-friendly and do not require specialized training or equipment, they are relatively expensive and limited in distinguishing between different *Plasmodium* species, except for *P. falciparum*. If three consecutive days of tests show no presence of parasites, malaria can generally be ruled out [18].

Treatment

Malaria is curable if treated promptly and effectively. Historically, quinine from the bark of the Cinchona tree was the primary treatment. However, *P. falciparum* has developed resistance to commonly used antimalarials such as Fansidar and chloroquine, leading to increased use of combination therapies. Artemisinin, derived from the plant *Artemisia annua*, is currently one of the most effective antimalarials, often combined with other drugs like Fansidar or mefloquine. Despite these advances, the spread of drug-resistant strains, particularly in Southeast Asia, poses a significant challenge. Additionally, there are no clinically approved malaria vaccines, although several of them are under development [19].

Pathophysiology

Malaria's pathophysiology is influenced by both parasitic and host factors, particularly affecting glucose homeostasis. Factors such as parasite metabolism, fever, hormonal changes, inflammatory mediators, and gastrointestinal disturbances contribute to a trend toward hypoglycemia, which can progress to hyperglycemia in severe cases. Insulin, the primary hormone regulating plasma glucose, is counteracted by other hormones like glucagon, thyroid hormones, and cortisol. In malaria, *Plasmodium* parasites significantly alter the red blood cell (RBC) membrane, which lacks insulin receptors and relies on glucose transporter 1 (GLUT 1) for glucose uptake [4].

Parasitized RBCs undergo dramatic transformations, with the parasite inserting transmembrane proteins into the RBC membrane. These proteins, including RESA, KAHRP, MESA, and PfEMP1, remodel the RBC for increased virulence and facilitate nutrient exchange between the parasite and host cell. This remodelling is crucial for parasite survival, as it maintains the integrity of the RBC membrane to allow glucose transport and other exchanges necessary for the parasite's growth and maturation [20][21][22][23]

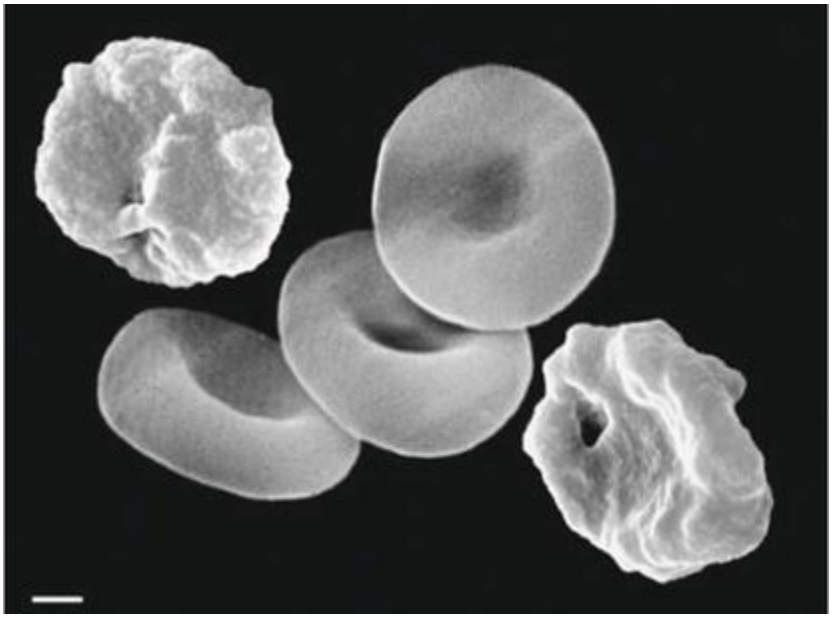

Figure 2: Scanning electron micrograph of normal RBC and Plasmodium falciparum pRBC. [23]

Impact of Malaria on Glucose Levels

Hypoglycemia in Malaria: *Plasmodium* parasites, particularly *P. falciparum*, have a high metabolic rate, consuming significant amounts of glucose. This increased consumption can lead to hypoglycemia, especially in severe malaria cases. The immune response to infection releases cytokines that can disrupt normal glucose production and regulation, further contributing to hypoglycemia. Malaria can impair liver function, reducing its ability to produce glucose via gluconeogenesis. This impairment is exacerbated by the cytokine response and the parasite's direct impact on liver cells [24].

Hyperglycemia in Malaria: The stress response to infection can increase cortisol and catecholamines, leading to hyperglycemia. This is more common in the early stages of infection or in individuals with a preexisting risk of diabetes. Infection can induce insulin resistance due to inflammatory cytokines, leading to less effective glucose uptake by cells and elevated blood glucose levels [25].

Impact on Diabetic Patients: Diabetic patients with malaria may experience fluctuations between hyperglycemia and hypoglycemia, requiring close monitoring and adjustment of antidiabetic medications during treatment and the combined stress of malaria and diabetes increases the risk of complications, such as ketoacidosis in type 1 diabetics or hyperosmolar hyperglycemic state in type 2 diabetics [26].

Role of Malaria Parasite in Glucose Metabolism

The *Plasmodium* parasite significantly impacts glucose metabolism during infection. Residing within RBCs, the parasite consumes glucose as its primary energy source, disrupting glucose homeostasis and transport. *P. falciparum*, the most lethal species, increases glucose uptake by inserting its own transmembrane proteins into the RBC membrane, enhancing glucose transport via GLUT 1. The parasite's high metabolic demands contribute to hypoglycemia in infected individuals [27].

The parasite relies on glycolysis for ATP production, making the glycolytic pathway essential for its survival. Targeting specific enzymes within this pathway could potentially

inhibit the parasite's growth and reduce disease severity. The parasite also scavenges various carbon sources and nutrients from the host cell, further impacting host metabolism and exacerbating symptoms.

Potential Biomarkers for Glucose-Related Malaria Complications

Identifying biomarkers for glucose-related complications in malaria can significantly enhance disease management and prognosis. Blood Glucose Levels (Low blood glucose levels (<2.2 mmol/L or <40 mg/dL) are critical markers for severe malaria, particularly in children and pregnant women, elevated blood glucose levels may indicate a stress response or underlying diabetes, complicating malaria treatment [2]. Elevated lactate levels (>5 mmol/L) are associated with severe malaria and poor prognosis, indicating metabolic acidosis and tissue hypoxia, often accompanying severe hypoglycemia [28]. Dysregulation of insulin levels can occur in severe malaria. Hyperinsulinemia may serve as a compensatory mechanism for hypoglycemia, while low insulin levels may indicate severe metabolic disturbances [29]. As a marker of insulin production, C-peptide levels provide insight into pancreatic function and insulin secretion in malaria patients, with altered levels indicating issues with insulin production or secretion. HbA1c reflects long-term glucose levels and can help identify patients with pre-existing diabetes or chronic hyperglycemia, influencing malaria outcomes. Elevated levels of TNF-α and IL-6 are associated with severe malaria and can influence glucose metabolism, leading to insulin resistance and hyperglycemia [30]. Elevated free fatty acids (FFAs) can indicate metabolic stress and contribute to insulin resistance, complicating glucose management in severe malaria [31].

Impact of Antimalarial Drugs on Glucose Levels

Antimalarial drugs can have varying effects on glucose levels. Quinidine and synthetic antimalarials like amodiaquine can raise plasma glucose concentrations. For example, in patients given quinidine, plasma insulin levels increased significantly, while plasma glucose concentrations decreased. In contrast, other antimalarials like chloroquine, amodiaquine, mefloquine, and halofantrine do not stimulate insulin release, which can be advantageous in avoiding hypoglycemia in severely ill patients [16].

Glucose-6-phosphate dehydrogenase (G6PD) deficiency, common in populations exposed to malaria, can cause hemolysis after administration of certain antimalarial drugs like primaquine. This highlights the importance of considering individual factors when choosing antimalarial treatments to manage potential risks. Successful malaria treatment involves supportive measures alongside specific antimalarial drugs, with careful consideration of the metabolic side effects of these treatments [32][33].

Monitoring glucose levels in malaria patients is crucial due to the high risk of hypoglycemia, a serious complication closely linked to increased morbidity and mortality. Hypoglycemia is particularly dangerous in severe malaria, often accompanying conditions like cerebral malaria (CM) that impair consciousness. The case fatality rate for malaria-related hypoglycemia can range from 3.3% to 61.5%, making early detection and treatment essential [34].

The World Health Organization (WHO) recommends capillary glucose measurements upon admission and every four hours for severe malaria cases. However, this approach may underestimate the true incidence of hypoglycemia, as studies show continuous glucose monitoring detects more episodes than intermittent checks. The impact of these missed hypoglycemia episodes on long-term outcomes like neurological damage remains unclear, highlighting the need for more specific guidelines to improve the management of severe malaria [35].

Conclusion

There is a significant link between glucose levels and malaria with evidence suggesting that glucose levels can impact on parasite growth, disease severity and the susceptibility of individuals to malaria infection. Hypoglycemia is a frequent and dangerous complication in malaria, particularly severe plasmodium malaria which affects various age grades especially children and pregnant women. It is associated with high mortality and morbidity, including increased risk of cerebral malaria and neurological impairment. Prompt recognition and treatment of hypoglycemia is critical in the management of severe malaria.

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