Chapter 3

Malaria Pathophysiology as a Syndrome: Focus on Glucose Homeostasis in Severe Malaria and Phytotherapeutics Management of the Disease

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Abstract

Severe malaria presents with varied pathophysiological manifestations to include derangement in glucose homeostasis. The changes in glucose management by the infected human host emanate from both *Plasmodium* parasitic and host factors and/or influences which are aimed at creating a proliferative advantage to the parasite. This also includes morphological changes that that take place to both infected and uninfected cells as structural alterations occur on the cell membranes to allow for increased nutrients (glucose) transportation into the cells. Without the availability, effective and efficient intervention there is a high cost incurred by the human host. Hyperglycaemia, hypoglycaemia and hyperinsulinemia are critical aspects displayed in severe malaria. Conventional treatment to malaria renders itself hostile to the host with negative glucose metabolism changes experiences in the young, pregnant women and malaria naïve individuals. In malaria, therefore, host effects, parasite imperatives and treatment regimens play a pivotal role in the return to wellness of the patient. Phytotherapeutics are emerging as treatment alternatives that ameliorate glucose homeostasis alternations as well as combat malaria parasitaemia. The phytochemicals e.g. triterpenes, have been shown to alleviate the "disease" and "parasitic" aspects of malaria pointing at key aspects in ameliorating malaria glucose homeostasis fallings-out that are experienced in malaria.

Keywords: malaria, glucose homeostasis, hypoglycaemia, hyperglycaemia, GLUT1, GLUT4, HfHT, hyperinsulinemia, phytochemicals, asiatic acid, triterpenes

1. Introduction

Malaria is one of the most prevalent parasitic diseases ever to infect the human being with causalities exceeding 200 million a year of mostly children <5 years of age, pregnant women, and people form none-endemic areas who happen to be non-immune to the disease [1]. Continuous and frequent infections for the Plasmodium parasites from holoendemic areas induces immune semi-protection to the malaria disease mostly the malaria naïve visitors [2]. There are several parasites species of the *Plasmodium genus* (>100 species) but only a few have the correct virulence to cause malaria in humans. These include *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale*, *Plasmodium malariae* and the zoonotic *Plasmodium knowlesi*. These parasites give diverse malarial syndromes with *P. falciparum* giving the most virulent and fatal disease. Even with this infection, the disease poses varying degrees of severity with one extreme displaying an asymptomatic blood smear erythrocytic phase positive infection and the other extreme displaying severe malarial disease with high mortality risk [3]. Severe malaria (SM) manifests as clinical and pathological heterogeneous complications that differ in the rate of occurrence, age of the subjects and geographical distributions [4] following disease patterns and time course that may be predictable or completely obscure to researchers, clinicians and the subjects alike.

While cerebral malaria (CM) ranks as the most dangerous, with the highest fatality of all forms of SM, severe malaria anaemia (SMA) [5] follows a close second in sub-Saharan Africa. Hypoglycaemia [6–8], hypotension, acute kidney injury (AKI) [9], acute respiratory distress syndrome (ARDS) and acute lung injury (ALI) [10], pulmonary oedema, non-respiratory acidosis (nRD) and hyperlactaemia [11–13], bleeding and blood clotting irregularities with thrombocytopaenia, aberrant inflammatory response [14] and pre-hepatic jaundice are often presented in SM although at varying incidence and prevalence [15]. The pathophysiology and parasitic influences are indeed variable in individuals. However, in all complications there is a base line of metabolic and homeostatic dysfunctions that have been observed over time, especially of glucose and associated processes that seem to be ameliorated by agents trained at the "disease" aspect of malaria [8, 10, 16] as compared to the "parasitic" influences.

Several factors tend to influence glucose homeostasis in malarial infections. These include parasite metabolism, malarial pyrexia, human host hormonal changes, inflammatory soluble mediators (cytokines and chemokines), natural immunological responses irregularities, malarial anorexia and cachexic tendencies and gastrointestinal disturbances [11]. There is a general trend observed in the glucose homeostasis that follows a tendency towards hypoglycaemic phenotype which, without appropriate intervention, evolves into end stage disease hyperglycaemia. Insufficient hormonal effectiveness associated with immunological-inflammatory aberrations of severe malaria play a pivotal role in the malaria-induced glucose homeostasis decline.

Insulin is the foremost and most important hormone that is involved in the plasma glucose homeostasis and is counter regulated by almost other hormones that are involved in carbohydrate metabolism such as glucagon, thyroid hormones (thyroxine and triiodothyronine) growth hormone, cortisol, somatomedins, somatostatins, gastrointestinal secretin of the other hormones.

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In malaria, the intracellular-erythrocytic malaria parasite partly influences glucose homeostasis. Generally, the red blood cell (RBC) or erythrocyte is categorised as an insulin-independent tissue having no plasma membrane insulin receptors (IR's). Glucose uptake by the RBC's is transported across their plasma membrane through the facilitation of glucose transporter 1 (GLUT 1). There is a significant and dramatic transformation of parasitized RBC's (pRBC's) plasma membranes after invasion by the *Plasmodium* parasite through insertion of various transmembrane proteins forming knobs which are interactions between the host and parasite proteins. These structures are formed from pRBC proteins such as spectrin and actin combining with parasite derived molecules such as ring-infected erythrocyte surface antigen (RESA), knob associated histidine-rich protein (KAHRP), mature parasite-infected erythrocyte surface antigen (MESA), *Plasmodium falciparum* erythrocyte membrane protein 1 (PfEMP1) and PfEMP3 [17]. These protein remodel the pRBC for increase parasite virulence, expedite the movement of parasite requirements into and discarded products out of the pRBC to meet the needs of the growing intra-erythrocytic food vacuole enclosed parasites [18]. There is a distinct change that occurs in the cell membrane structure and function in pRBC's with targeted disruption parasite proteins genes invariably leading to changes in membrane rigidity and, cytoadherence and glucose transportation [19, 20] (**Figure 1**). The resultant changes in the cell membrane is necessary to maintain the structural formation or remodelling necessary for exchanges between the food vacuole and the host cell cytoplasm. Channels formed in the plasma membrane need to be maintained without disruption until the parasite intra-erythrocyte parasite has matured. This also means the mechanism for glucose transport into the pRBC's are also maintained.

The main parasitic energy source is glucose. The *P. falciparum* hexose transporter (*Pf*HT), which transports both glucose and fructose, is the main transporter of glucose shuttle from the cytoplasm to the parasitophorous vacuole [15, 21–23]. Within the parasite vacuole, glucose concentration may be higher than that in the pRBC due to the efficient transport of the *Pf*HT driving hypoglycaemia to some extent, although it was thought to be an passive action before [24].

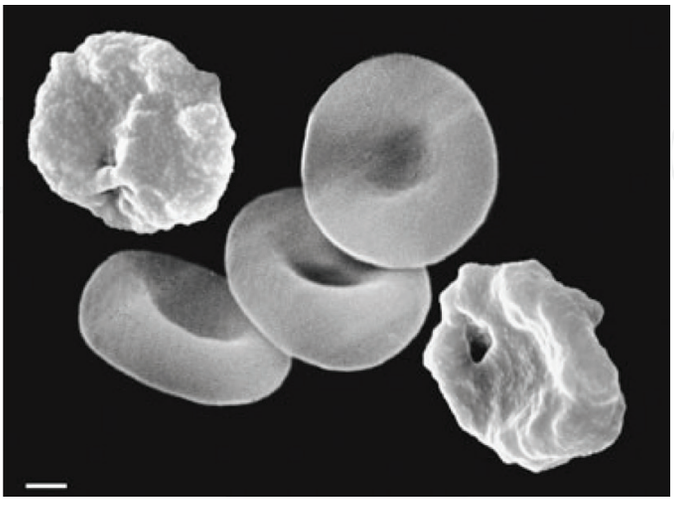

Figure 1. Scanning electron micrograph of normal RBC and *Plasmodium falciparum* pRBC. The three normal RBC at the centre appear regular and smooth and have a biconcave structure. In contrast the two peripheral pRBC have an irregular and rough surface and have lost the biconcave structure. (Published with permission, Professor David Ferguson, Oxford University, Oxford, UK). Scale bar = 1 μm.

Also, pRBC anchor protein glycosylphosphatidylinositol (GPI) have an insulinomemetic effect that may also drive hypoglycaemia. However, insulin resistance seen in end-stage SM, fuels hyperglycaemia where insulin-dependent tissues like muscle and adipose tissue may be deficient of glucose intracellularly in the face of hyperinsulinism depicting glucose disturbances during SM [25]. Counter regulatory glucose metabolism also has been shown to increase gluconeogenesis in SM without necessarily increasing their activities due to the tissue resistance to insulin [26]. In addition to hormonal effects, inflammatory mediators play a crucial role in the hyperglycaemia experienced in SM.

It is imperative to explain the normal glucose homeostasis before a description of the pathophysiology of malarial glucose metabolism may be attempted. Here the process by which aberrant glucose metabolism occurs in SM is explored with critical emphasis on how management of the malaria disease may be useful in averting glucose homeostasis derangements.

1.1. Glucose homeostasis

Human blood glucose concentration control is one of the most tightly and acutely physiological processes. Glucose utilisation, storage and remarshalling takes place in diverse number of tissues to include in the blood. When carbohydrates are consumed, blood glucose diminishes in concentration through an insulin-stimulated glucose transport process into the skeletal muscles and adipose tissue for storage. Glucose is stored as glycogen in the skeletal muscles which is subsequently oxidised to provide energy following an active transport process.

Glucose transporter 4 (GLUT4) is the key player in modifiable whole-body glucose homeostasis and balance. Even after a huge caloric intake, elevated glucose concentrations are promptly restored to concentrations between 5 and 6 mmol/L which would vary to slightly lower concentration in times of long term starvation or considerable food intake deprivation. This way, severe dysfunctions induced by hypoglycaemia such as loss of consciousness and peripheral tissue noxiousness of chronic diabetes mellitus are forfended. In malaria, however, GLUT1 is more prominent in glucose transport in both the pRBC and the hepatocyte although GLUT2 is the resident transporter of glucose in the liver cells.

2. Glucose transporter 4 (GLUT4)

To modulate the glucose homeostasis, an exogenous glucose load transport into skeletal muscles is mediated by the solute carrier 2A4 (SLC2A4) gene coded protein GLUT4 which is a 12-transmembrane domains containing sugar transporter. GLUT4 is one of the 13 sugar transporter proteins (GLUT1-GLUT12 and HMIT) which are encoded in the human genome [27] which catalyse hexose transport across cell membranes through ATP-independent, facilitative diffusion mechanism [28].

There is a varied display of kinetics and substrate specificities amongst the sugar transporters with GLUT5 and GLUT11 specialising in the transport of fructose. There is a high expression of GLUT4 in adipose tissue and skeletal muscle although a selective cohort of other transporters are also present with GLUT1, GLUT5 and GLUT12 significantly contribute to the glucose uptake by muscle tissue [30, 31] while GLUT8, GLUT12, HMIT are also expressed by adipose

tissue [27, 32]. GLUT4 remains in the cytoplasm when it is in its inactivated state making a unique and characteristic rapid response when plasma glucose concentrations are increased with an acute redistribution to the plasma membrane under the influence of insulin [33]. The cytoplasmic domains of GLUT4 provides the distinctive plasma membrane mobilizations capabilities of this sugar transporter in that it contains a unique sequence in its N- and COOH terminals (**Figure 2**). In the N-terminal GLUT4 has a critical phenylalanine residue [34], a dileucine and acidic motifs in the COOH terminus, which motifs directs kinetic facets of endocytosis and exocytosis recycling trafficking coordination [35, 36]. GLUT4 plays a critical role in both insulin signalling and plasma membrane trafficking [37].

Stimulation of GLUT4 recruitment to the surface of plasma membranes of muscle and adipose cells is carried out by insulin and exercise in a non-transcription or translation dependent process [38, 39]. However, the signalling mechanisms that are initiated by these two physiological stimulations leading to the translocation of GLUT4 and the uptake of glucose are distinct and separate [40, 41] as shown by the diagrammatic representation in **Figure 3**. This has a profound implication on the hyper-muscular/physical activities (physical movement or malaria pyrexia) and hyperinsulinemia that tend to be associated with malaria which may lead to and or worsen hypoglycaemia of malaria.

In the canonical insulin signalling pathway, activation of the insulin receptor (IR) tyrosine kinase triggers the process leading to insulin receptor substrate proteins (IRS) tyrosine phosphorylation and their recruitment of PI 3-kinase. PI 3-kinase catalyses the conversion of phosphatidylinositol (4,5)P2 to phosphatidylinositol (3,4,5)P3 (PIP3), which triggers protein kinase Akt activation through intermediate proteins PDK1 and Rictor/mTOR [42, 43].

A number of cellular stress signals enhance glucose uptake by skeletal muscle. Free fatty acids (FFT's), increased cytokines, endothelial reticulum stress, hypoxia, oxidative stress,

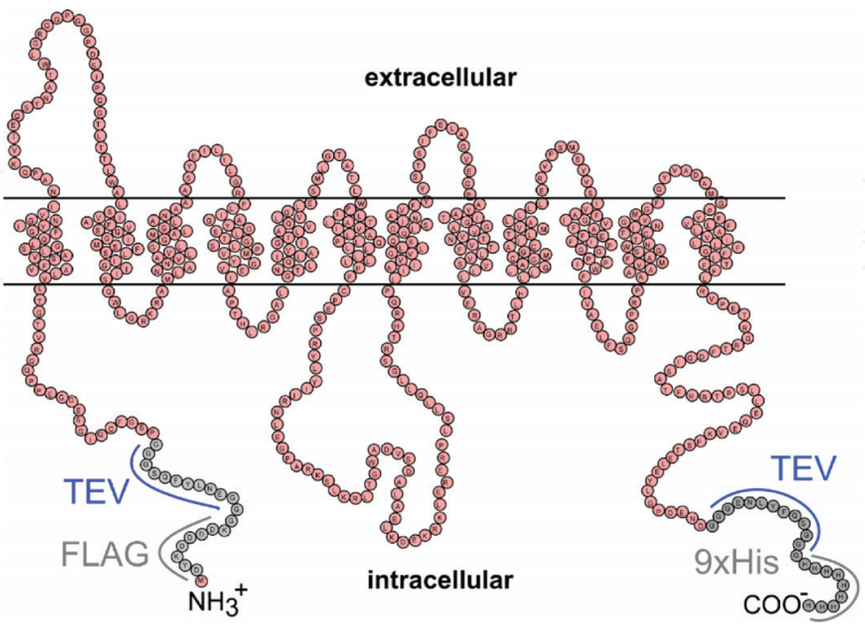

Figure 2. Predicted topology map of GLUT4. The membrane topology was predicted using the TOPCONS web server for consensus prediction of membrane protein topology and signal peptides [29]. Grey amino acids were added for aiding purification and removal of purification tags.

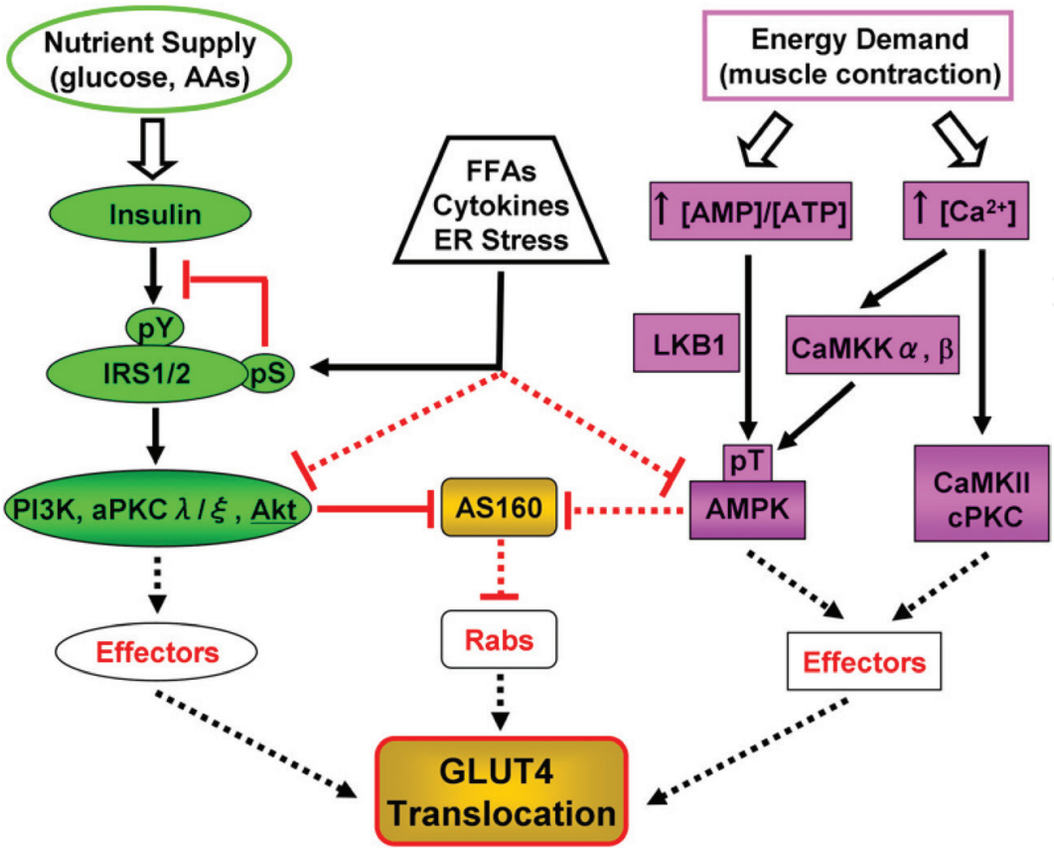

Figure 3. Convergence of signalling pathways: initiated by insulin and exercise leading to GLUT4 translocation insulin signalling through the PI 3-kinase pathway and muscle contraction through both elevated AMP/ATP ratios and intracellular [Ca^{2+}] leads to activation of downstream protein kinases (Akt, aPKCl/z, AMPK, CaMKII cPKC) that phosphorylate putative effectors that modulate steps in the GLUT4 trafficking pathways. Negative regulation of these pathways by fatty acids, cytokines, and endoplasmic reticulum stress responses are observed in obesity and diabetes, contributing to insulin resistance. Dashed lines imply hypothetical pathways not yet experimentally verified.

inhibitors of cellular metabolism, decreasing cellular energy supply and increasing AMP/ATP ratios (**Figure 3**) tend to increase glucose uptake by muscle cells. These effectors of glucose uptake are readily found in malaria infection as both a result of parasite and host mechanism for survival. In adipocytes and muscle cells, hyperosmotic stress, a common feature of SM, promote GLUT4 translocation by activating AMPK and Gab-1 dependent signalling pathway, respectively [44]. Furthermore, osmatic shock activates Akt substrates, which promotes GLUT4 exocytosis to the plasma membranes of adipocytes increasing glucose uptake [45] and in malaria, inducing hypoglycaemia. In a paradox of some sorts, chronic hyperosmotic stress causes insulin resistance in isolated or cultured adipocytes as shown by increased insulin concentration and hyperglycaemia. Apparently, mTOR signalling pathway arbitrates this hyperosmolality-induced hyperinsulinemia a phenomenon that has been observed in end stage SM disease in animals where a cycle of hyperglycaemia breeding more hyperosmolality leads to more insulin resistance [44]. An intricate mTOR signalling, involving an intricate negative feedback mechanism, aiming at insulin and AMPK signalling pathways have been revealed [46]. Further to that, GLUT4 compromised sensitivity to insulin signalling pathway is a common feature of obesity and diabetes mellitus mediated by fatty acids activity [47],

cytokines activity [48] and endoplasmic reticulum stress response [49] (**Figure 3**). Activation of stress protein kinases that are involved in the phosphorylation of IRS proteins serine residues attenuate tyrosine phosphorylation of IRS by insulin causing the negative regulation of GLUT4 translocation to the plasma membrane surface (**Figure 3**). These processes are inimical to glucose homeostasis as does end stage non-reversible SM [15].

3. Glucose transporter I (GLUT1) and it involvement in malaria

Most cell depends on glucose as a key substrate for a variate of metabolic processes that are necessary for energy production and cellular building blocks. Transportation of glucose, and other carbohydrates, into the cytoplasm of most cells is through a 14 member family of integral membrane glucose transporter molecules also known as solute carrier 2A protein which are sub-divided into Classes I–III [50]. Within this superfamily is the glucose transporter 1 a Class I facilitative glucose transporter expressed in the hepatocytes [51] with the highest expression being found in the membrane of the erythrocyte or red blood cells (RBC's) [52] and also influences the glucose uptake across the blood brain barrier [53]. GLUT1 has various functions in the body amongst which being a receptor for the human T cell leukaemia virus [54] and glucose transport in T-cells where it regulates infection by the Human Immunodeficiency virus [55] appear to be the most prominent ones besides its involvement with malaria infection in both the red blood cell and the hepatocyte [55].

The malarial parasite expurgates a uni-directional trajectory during its infection of the human being from the time the *Plasmodium sporozoites* are injected into the bite by an infected mosquito to the period of overt symptomatic infection. After crossing the hepatic endothelium, sinusoids and entering the liver, sporozoites transverse several parenchymal liver cells before finally invading one in which the productive asymptomatic exoerythrocytic forms (EEF's) differentiation takes place with the origination thousands of RBC's-infective merozoites which are released into the circulation to start symptomatic infection [56].

Production of adenosine triphosphate (ATP) [24], the energy source of the blood stage merozoites and other erythrocytic stage parasites, is derived from glycolysis of which a model now exist for the *Plasmodium falciparum* [57] showing it as an equilibrated than an active process in the parasite [24]. GLUT1 has been shown to transport glucose from human plasma to the erythrocyte cytoplasm [58] from where the parasite encoded facilitative hexose transporter (PfHT) [59], which limits glucose entry into parasite's glycolysis [60]. Thus, the PfHT targeting in novel malaria treatment is plausible undertakings [61] seeing that in the murine malaria model, *P. berghei*, orthologous hexose transporter (PbHT), is expressed throughout the parasite's development in the mosquito vector, during hepatic and transmission stages [62]. When the PbHT are inhibited (by compound 3361), a drastic inhibition of growth of the hepatic parasitic stage of the *P. berghei* was observed, showing that glucose uptake is crucial in infected hepatocytes for both energy and nutrients supply for the parasite [61]. In vitro studies have established that the key parameters in the development of liver stage parasites were the glucose concentration in the cell culture media and utilisation of glucose by the Plasmodium liver stages [63]. Glucose requirements during the course of parasite development in the

hepatocyte and the host cell molecular receptors involved with the uptake of glucose by the cells was studied in this work. *P. berghei* infection resulted in the depletion of ATP with subsequent translocation of GLUT1 from the cytoplasm to the membrane surface of infected hepatocytes which resulted in significantly higher glucose uptake compared to non-infected cells. Furthermore, glucose plays in a critical role during the development of the liver stage infection, modulating the Plasmodium development in the EEF's [52].

3.1. Effect of glucose on hepatic murine malaria infection model

Experiments have been carried out to the effect of glucose in the propagation of malaria disease in vitro and in vivo. Inclusion of various glucose from 1.25 to 20 mM in a hepatic cell (Huh7 cells) line which cover the physiological glucose concentration range, 2.5 to 10 mM [64], unravelled that the increasing glucose concentrations availability 48 hours post infection (hpi) correlated with overall *Plasmodium* patent infection [52]. Using a parasite load marker and cell viability, luminescence intensity [65], investigators reported that concentrations of glucose <10 mM, which is the cell medium standard, significantly impairs hepatic *Plasmodium* infection while excess glucose does not affect cell viability but is decreased at 2.5 and 1.5 mM glucose concentrations [52]. A flow cytometry-based approach using green fluorescent protein (GFP)-expressing *P. berghe*i parasites [66] was used to determine the number of infected hepatic cells and parasite growth. The ability of parasite to transverse or invade hepatic cells was not dependent on glucose concentration within the initial 2 hours when sporozoites hepatocytes invasion was virtually complete [66], but after 48 hpi glucose concentration was important with concentrations of >20 mM showing the higher parasite development and lower at concentrations of glucose lower than glucose physiological range.

Furthermore, the parasite size correlates well with glucose concentration (very small parasites <50 μm^2 and fewer infected cells) while increasing glucose concentration (10–20 mM) favoured increased parasite sizes (>200 μm^2) and number of infected cells [52]. While hepatoma cells (Huh7 cells) depend highly on glucose uptake for ATP glycolysis synthesis [67], primary liver cells store glucose as glycogen from which ATP is obtained through oxidative phosphorylation. However, regardless of the hepatocyte source, parasite proliferation depends greatly on glucose concentration with increased glucose uptake highest in plasmodium-infected hepatocytes, parasite development and survival [52].

To demonstrate the link between hepatic stage parasite development, plasmodium replication and increased glucose uptake, fluorescent glucose analogue, 2-deoxy-2-[(7-nitro-2,1,3-benzoxadiazol-4-yl)amino]-D-glucose (2-NBDG) [68, 69], has been used. At 30 hpi set point and onward, significant glucose uptake by the hepatocyte and the parasite increases in cells infected by viable parasites as compared to non-infected cells and infected cells with non-replicating cells [52, 66].

Glucose uptake depends on several influences that include feeding and fasting status, exposure to heat or cold [70], physical activity [71], oxidative stress [72], hepatic diseases (steatosis, non-alcoholic fatty acid liver disease, hepatitis C virus infection) [73]. However, none of the stress-inducing factors contribute to the increase in glucose uptake besides the presence of malaria parasites in infected hepatocytes in any comparable measure which indicate Plasmodium parasite has a specific and unique way for handling glucose homeostasis.

Actually, experiments carried out have invariably shown that the malaria parasites induce glucose uptake that is not a non-specific response to stress or to infection but a specific and enhanced marked glucose uptake with a calculated end. Other intracellular organisms have been reported to have a dissimilar effect on glucose uptake which makes the *Plasmodium* glucose metabolism rather inimitable. *Toxoplasma gondii* does not depend on glucose uptake from the host [74]. On the other hand, cellular glucose uptake is suppressed through downregulation of cell surface glucose transporters expression during active hepatitis C virus replication [75]. This, then, characterises Plasmodium infection as an exceptional intracellular parasite glucose homeostasis machinery whose aetiology and mechanism of action has insidious connotations to human survival seeing that the parasites life cycle is intimately associated to and manipulates human biology at will.

3.2. Specific indications of GLUT1 implication in malarial parasite-infected-cell glucose uptake

In experiments that sought to ascertain by which specific glucose transporter was uptake enhancement possible, genes for the expression of 5 transmembrane glucose transporters were sequentially down-regulated and the effect of this measured in Huh& cell lines. Class I GLUT genes (GLUT1-4) and GLUT9, which is a HepG2 hepatoma cells (and Huh7 equivalent) glucose influx regulator [76], were screened for their influence of glucose uptake in malaria parasite-infected cells through silencing each gene at a time and determining the parasite load [52]. The GLUT1 gene knock down (KD) resulted in the most significant decrease in malaria parasites in these experiments. This did not only show that glucose uptake was important for parasite development but also that GLUT1 was responsible for the glucose uptake that causes enhanced parasite growth in the liver cells. Down-regulation of GKUT2, which the major glucose transporter in hepatocyte did not affect the glucose uptake in cells holding actively replicating parasites as it was observed that GLUT1 KD did not affect glucose uptake in non-infected cells [52]. Chemical inhibition of GLUT1 (adding 100 μM WZB117 to cell culture) in both hepatoma cells and primary hepatocytes has been reported as having the same decreased effect on glucose uptake, parasite development and replication as does GLUT1 KD.

3.3. Glucose transporter 1 expression in *Plasmodium*-infected cells

A hypothesis that the enhanced glucose uptake in *Plasmodium*-infected cells may due to an over expression of the GLUT1 in malaria is an intruding and tempting approach to explaining the increased glucose uptake that is associated with malarial hypoglycaemia. However, Meireles et al. [52] monitored the expression of the GLUT1 in infected Huh7 cells, at increasing time periods hpi, revealed a different and amazing phenomenon contrary to the hypothesis. No significant increase in GLUT1 mRNA was observed between infected and non-infected cells using fluorescence-activated cell sorting (FACS) technique [77] and analysing with quantitative real-time polymerase chain reaction (qPCR) and GLUT1 specific primers. This, therefore, means that the amplified glucose uptake by Plasmodium parasite-infected cells does not emanate from genetically induced GLUT1 synthesis but from the circulating pool of already existing glucose transporters.

As *Plasmodium* parasites increase in number in the infected cell, there is a proportional depletion of cytoplasmic ATP overall. It is necessary that GLUT1 to remain inactive during normal

or reduced cellular energy demands or else it will derive hypoglycaemia. This necessary regulation occurs through the binding of ATP by GLUT1 cytoplasmic pockets [78] which causes conformational changes to the molecule inhibiting glucose transportation [79]. In a competitive binding principle, Adenosine monophosphate (AMP) and Adenosine diphosphate (ADP) counteract the ATP-induced conformational modulation by binding to the same site activating the glucose GLUT1-mediated transportation [78]. True enough, intracellular ATP has been reported to be significantly decreased in *Plasmodium* parasite-infected cells as compared to non-infected cells validating presumably decreased ATP/ADP/AMP ratio of malaria infection that drives conformational changes in GLUT1 [78–80]. The sequence of events in GLUT1 metabolism in malaria infection tends to follow a transcendence guided by the depletion of intracellular ATP, which activates the GLUT1 proteins and subsequent translocation to the infected cell membrane where it enhances glucose uptake driving the hypoglycaemia pathophysiology of malaria.

4. Comparison of GLUT1 and GLUT2 involvement in glucose uptake in malaria

The significant increase in infected liver cells through an enhanced action and translocation of GLUT1 to the surface membrane looks like the key mechanism by which Plasmodium parasites acquire the source of energy that is obligatory for their replication and survival. The ability to transport glucose across plasma membranes is a feature in most cells that make the hexose a ubiquitous common currency of metabolism [50]. Whereas GLUT2 represents the major glucose transporter, (uptake and release, in hepatocytes during the fed and starved state, respectively [50, 81], GLUT1 is also transcribed and expressed in the liver cells of the periportal and perivenular hepatic areas [82].

There are disparities between GLUT1 and GLUT2 in terms of their capacity to handle and affinity for glucose. GLUT2's capacity and affinity for glucose are inversely related, i.e. high capacity and low affinity shown by a Km value (glucose concentration at which transport is half of its maximum value) of 17 mM [83]. The Km value of GLUT1 is higher and much closer to that of the PfHT at 3 mM [83] as compared to 1 mM [23]. Therefore, GLUT1 may be better matched for hexose supply to the *Plasmodium* parasite in malarial hypoglycaemia where glucose concentration decreases towards the Km of the solute transporter.

There is a restriction of GLUT1 to membrane of liver cells that are proximal to the hepatic venule during basal states, although the transporter is expressed by all hepatocytes [50, 51, 82]. There is a decreasing gradient of oxygen and glucose as blood flows from the portal to hepatic venule due to the unidirectional perfusion of the hepatocyte plate [84]. This environment of reduced circulating glucose concentration [85] and hypoxia [86] are instrumental and conducive to the enhanced membranous expression of GLUT1. Hypoxia boosts liver stage malarial infection as much as does an activator of hypoxia inducible factor-1α (HIF-1α) or the hypoxia mimetic $CoCl_2$ [87]. On the other hand, increased concentrations of HIF-1α have been shown to upregulate GLUT1 expression [88] and $CoCl_2$ is known to enhance the translocation of the hexose transporter to the plasma membrane [52, 89]. Overall, GLUT1-mediated

glucose transport seems to provide the important linkages defining the preferred tendency of *Plasmodium* parasites in infecting hypoxic hepatocytes and red blood cells or inducing hypoxia as a driver of enhanced infectivity.

5. Mode of action of GLUT1 in glucose transport

Consequent to the extensive replication of the Plasmodium parasite in hepatocyte is the depletion of intracellular glucose concentration and subsequently concentration of ATP as well. The compensatory mechanism is an increase in glucose uptake. This may either result from activation of GLUT1 transporters at cell membrane as a result of AMP-dependent conformational alterations or from the GLUT1 translocation to the plasma membranes towards parasite final development stages [52]. The resultant momentous increase in glucose uptake during malarial infection does not only affect *Plasmodium* infected cells. Non-infected cells within the immediate environ of the infected cells also experience a glucose and energy deficit that tends to trigger similar glucose uptakes, albeit at inferior response. A comparable slight decrease in intracellular ATP and increase in translocation of GLUT1 with concomitant slight increase in glucose uptake in non-infected cells although it is still not clear what mechanisms are involved in the regulation of GLUT1's translocation or activation [52]. Activation of pre-existing GLUT1 on the plasma membranes which enhance glucose uptake has been shown to be associated with stimulation of AMP-activated kinase activity [90]. Also, GLUT1 translocation to the plasma membrane has been shown to be prompted by insulin and ischaemia (GLUT4 too) [91] in a manner dependent on a phosphoinositide 3-kinase (PI3K) [92]. Captivatingly, down-regulation of the α1 and α2 subunits does not seem to affect parasite development and glucose uptake by parasite-infected cells [52]. Furthermore, insulin addition or inhibition of PI3K with Wortmannin [93] did not seem to have a negative effect on infection and infected cell glucose uptake [52]. Protein kinase C phosphorylation of GLUT1 generated rapid glucose uptake and heightened plasma membrane localization of GLUT1 [94]. Speculation that the same mechanism may be at play in malarial glucose transported is well supported as the inhibition of GLUT1 result in reduced parasite replication parasite general infectivity.

The liver should be considered as a major site for postprandial glucose removal seeing that it holds a volume to remove 30–40% of glucose existing after ingestion [95] which could mean a huge glucose supply necessitating uptake that will support parasite growth. The association between increased risk from malaria infection with P. falciparum and diabetes type 2 (DM 2) is emerging [96] which may link GLUT1 glucose uptake as a possible instigator in these disease common trajectory. Sub Saharan Africa has seen an upsurge in DM 2 [97] in an area where malaria has been endemic for several years. Plasmodium parasites from infected DM 2 individuals have also been shown to have a higher infective capacity than those from non-DM 2 individuals [98] showing possibly the uptake of glucose by parasite infected cells plays a critical role in rendering the parasites more potent in transmission of the disease. As such, GLUT1 may be a druggable target for the treatment of malaria. The modulation of GLUT1 in cells that contain the malaria parasite provides leads towards the use of energy supply inhibition as a potential weaponry in the arsenal to combat malaria.

6. Interactions of glycosylphosphatidylinositol glucose homeostasis in malaria

The molecular interactions that brings about the activation of GLUT1 either on the plasma membrane or in the cytoplasm has been directly linked to the decrease of glucose and subsequently ATP from within the cell. Depletion of either glucose or ATP is associated with an increase in parasite replication and maturation. However, the triggering of the events in the decrease in glucose and ATP should a *Plasmodium* parasite initiative as other intracellular parasites discussed do not have such an inherent mechanism of glucose homeostasis.

Glycosylphosphatidylinositol (GPI) belongs to a class of glycolipids that are ubiquitous in eukaryotes where they display a number of biological effects [99]. In parasites, GPI's are particularly abundant as free lipids or as anchors of proteins. The GPI also formulate the majority of glycoconjugates in the intraerythrocytic *P. falciparum* where it anchors to the cell membrane functionally important parasite proteins like the merozoite surface proteins (MSP-1, MSP-2, MSP-4) [100]. *P. falciparum* GPI synthesis is a developmental stage-specific manner which is crucial for development and survival of the parasite [101] in the same way GLUT1 recruitment has been discussed elsewhere. The parasite GPI mediates hypoglycaemia through an insulin mimetic activity in a manner that increases GLUT1 population of the molecule on the surface membrane of *Plasmodium* infected cells via a tyrosine kinase dependent signal transduction [102] which puts this molecule at the centre of the processes leading to glucose and ATP depletion in the infected cell.

The GPI has also been reported to drive the pathophysiology of malaria through the ability to induce proinflammatory cytokines in the host which include tumour necrosis factor (TNF-α), interleukin-1β (IL-1β), nitric oxide (NO), interferon-γ (IFN-γ) [19, 103]. There is an up-regulation of intercellular adhesion molecule-1, vascular cell adhesion molecule-1, and e-selectin expression in vascular endothelial cells and increases leukocyte and parasite cytoadherence via tyrosine kinase dependent signal transduction that has been observed [104]. Most of these synthetic processes where GPI is involved are energy dependent and expend ATP whose source is glucose thereby indivertibly upregulate demand for the hexose by most cells interactive with the anchoring molecule. There are structural similarities between insulin second messengers (phosphatidylinositol-PI) and *Plasmodium* GPI which makes the insulin memetic effect of the membrane anchored glycolipid induce hypoglycaemia [105, 106]. The structural similarity will entail the activation of steps for glucose uptake by-passing the insulin receptor (IR) position of insulin signal transduction system. With the numerous GPI production capacity of the Plasmodium parasite, there arises a multitude of cellular GLUT1 activation that give increased glucose uptake into the cells. This brings about increased glucose availability to the growing parasites.

To bring this into perspective the relationship between the GLUT1 transporters and the subsequent uptake of glucose uptake by the parasite, the glucose transporter in the parasite's role in final glucose utilisation by the parasite needs be explored.

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7. Glucose transport in the intraerythrocytic *Plasmodium* parasites

With blood being a steady and abundant source of glucose, Plasmodium parasites find a haven and shelter of protection in the intraerythrocyte where they multiple and grow utilising glucose as the main energy source. When malarial parasites are deprived of glucose, ATP concentrations drop drastically and their hydrogen ion activity increased (pH drop) [107]. Parasite plasma membrane tend to depolarize with reduction in glucose concentration or reduced glycolysis or reduction of anaerobic fermentation of pyruvate to lactate, which are the systems by which parasites main sources of ATP [108]. Glycolysis provide faster ATP, although less efficient, than does oxidative phosphorylation at rates hundred times faster than the latter [109]. The malarial parasite does possess a glycolysis functionally disconnected branched TCA cycle which does not contribute to the Plasmodium energy homeostasis [110].

GLUT1, as mentioned elsewhere, delivers glucose to the cytoplasm of the RBC from the plasma in a passive down-a-concentration gradient facilitative process [111]. From the cell cytoplasm, the glucose has to transcend parasitophorous food vacuole (PFV) membrane which is highly porous to the solutes with molecular weights <1400 Da through high-capacity, low selectivity channels [112]. Uptake of glucose from the PFV is through a facilitative transport system carried out by, for *P. falciparum*, *Plasmodium falciparum* hexose transporter (PfHT) [PlasmaoDb accession number:PFB0210c] [24, 113].

There PfHT gene is a putative gene to the human glucose transporter gene with a homology to GLUT1. The predicted topology of PfHT protein has 12 transmembrane helices with both of its carboxy and amino terminals positioned in the cytoplasm of the cell (**Figure 4**). Functional characterisation of PfHT has shown that the parasite sugar transporter is a sodium-independent, saturable, facilitative hexose transporter [113] with a mechanistic difference with GLUT1 in the way it interacts with substrates [109]. Whereas PfHT transports D-glucose (Km-1 mM) and D-fructose (Km-11.5 mM), GLUT1 is selective for D-glucose (Km-2.4 mM). The affinity for glucose by PfHT, therefore means that the parasite may be acquire the hexose at very low plasma concentrations. This is also corroborated by the low Km of GLUT1, which transporter increases activity in infected cells, providing an efficient linkage between the infected and the parasite for glucose uptake. As shown in **Figure 4**, the unidirectional glucose uptake is favourable for parasite survival and maturation and can drive severe hypoglycaemia of severe malaria.

There has been a critical observation of hyperglycaemia occurring during severe malaria which has a penchant for fatal outcomes. In unpublished data, it has been observed that animals that develop hyperglycaemia with or without treatment or intervention tended to have adverse outcomes and hyperglycaemia in malaria was determined to be an end-point marker which required intervention. The molecular basis of hyperglycaemia development in a disease that hypoglycaemia is more of the norm than the exception finds its basis on a number of factors that include parasite infection, inflammatory host response and hormonal aberrations. These factors revolve around the gluconeogenesis and glycogenesis-glycogenolysis-glycolysis axis and how these play-out in malaria pathophysiology.

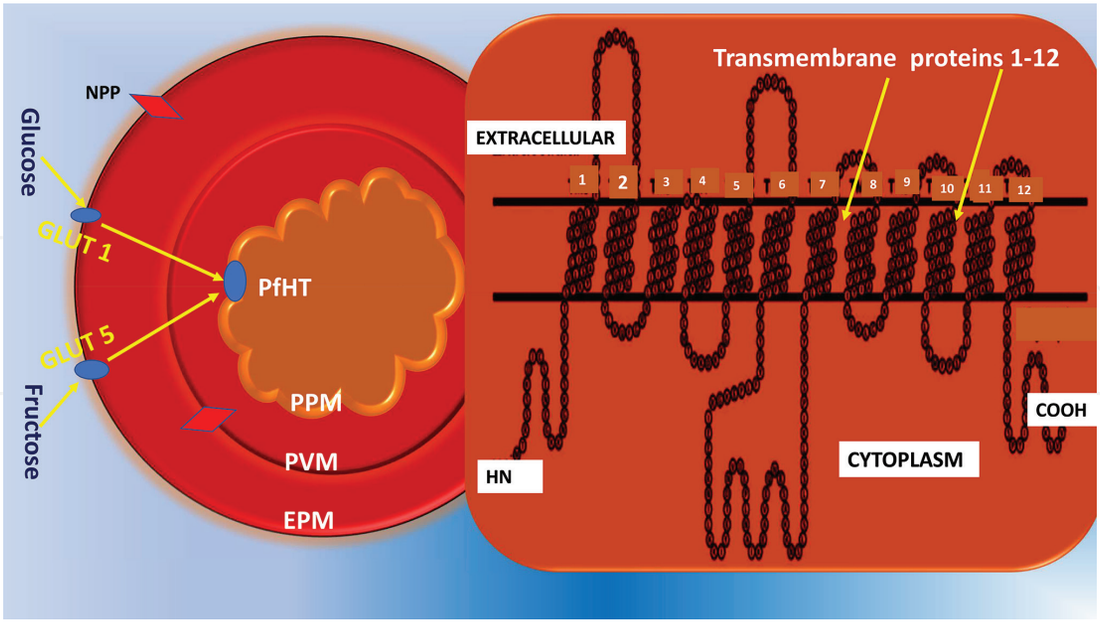

Figure 4. Hexoses uptake in Plasmodium-infected red blood cell shown in a schematic representation **A**. The EPM (erythrocyte plasma membrane), the PVM (parasitophorous vacuole membrane), the PPM (parasite plasma membrane) are shown. GLUT1, mammalian glucose transporter; GLUT5, mammalian fructose transporter; NPP, new permeability pathways (do not contribute significantly to the uptake of glucose [114]). **B** is the predicted topology of *Plasmodium falciparum* hexose transporter (PfHT) [113].

8. Production of glucose in malaria

Malaria has been associated with reduced glucose emanating from increased glucose utilisation by the growing intracellular parasites, especially towards the schizogony. Just as it has been shown that increased glucose trafficking is not as a result increased synthesis of GLUT1 but increased activation of the hexose transporter brought about depletion of ATP, there is no considerable doubt that there is increased glucose production in *P. falciparum* malaria which could be driven by the plasma hypoglycaemia. This same phenomenon was shown in adults infected with malaria that displayed increased glucose production [115].

Stimulation of gluconeogenesis is attributed to be the underlying reason for the increase in glucose production is severe malaria which leads to increased plasma glucose concentration. Concomitant with the rise in plasma glucose concentration is the rise in concentration of a hormone milieu comprising of plasma cortisol, glucagon and adiponectin. Surprisingly, the rise in the glucogenic hormones is not the cause of the increase in plasma glucose concentration.

In malaria, there is an increase in cytokine activities with TNF-α and IL-6 [116] which are known to have a stimulatory effect on glucose production indirectly through their influence on the secretion of glucose counter regulatory hormones [117]. Moreover, TNF-α stimulates the synthesis of prostaglandin synthesis by Kupffer cells and in turn, to complicate the picture somewhat, glucose production is inhibited by prostaglandin [117] showing an intricate mechanism involving glucose utilisation and production in severe malaria.

8.1. Malaria-related glucose clearance

Plasma glucose concentration is a balance between production and uptake or clearance which assist in the maintenance of the hexose within physiologic range. In cerebral malaria, showing severe malaria, there is an increase of glucose clearance rate by 42% and to a lesser extent in uncomplicated malaria increased by 9%. However, the overwhelming determinant of plasma glucose concentration in malaria is not through increased or decreased production but it is presumed to be through increased peripheral glucose uptake [115]. In theory, infected red blood cells have an increased glucose consumption of between 30 and 75 times than non-infected erythrocytes up to the time of trophozoite development of the parasite [118]. Increased glucose and lactate kinetics [6] and alanine metabolism have been reported in acute falciparum malaria [119]. The environmental stressor phenomenon brought about malarial illness impinges negatively on glucose utilisation with the overt outcome of glucose impaired metabolic processes like glycogenolysis and gluconeogenesis.

8.2. Malarial glycogenolysis

The glycogen mass in muscle and liver of infected animals has been observed to be much less as compared to control animals exposed to the same amount of food and water. Generally, the rate of glycogenesis in malaria is slow to absent as it is overridden by the quest to maintain euglycaemia in the face of hypoglycaemic threats and pressures. Glycogenolysis or glycogen breakdown to yield plasma glucose has more capacity than glycogenesis in both the liver and the muscles, however this occurrence may not cause hypoglycaemic tendencies of malaria. There is a hepatic autoregulation in as far as glycogen content is concerned in malaria, but its contribution to malarial hypoglycaemia is limited as compared to the increased clearance of glucose in malaria. Furthermore, glycogen, although lower in content in infected cases as compared to non-infected cases, is always present and not depleted completely in malaria [120].

8.3. Malarial gluconeogenesis

There has been a remarkable observation that, gluconeogenesis tends to increase with severity of the disease in *P. falciparum* infection and the more severe the disease the higher the stimulation degree. The previous consensus has been to the contrary of this observation in both pregnant and non-pregnant women with impaired gluconeogenesis as a recognised paradigm in malaria [121, 122]. The increased gluconeogenic stimulation is premised on the very important gluconeogenic precursor, the amino acid glutamine [123]. Children with acute malaria tend to have low concentrations of the amino acid [124] and will result in an increase rate of gluconeogenesis in a negative feedback mechanism rather than cause impairment. Furthermore, glycerol metabolism remains intact in malaria [125] and making the increase in gluconeogenic activity an perpetual enigma as fatty acid metabolism is also of no consequent in the aetiology of the glucose production process. Supply of gluconeogenic precursors, soluble chemical mediators and counterregulatory hormones remain key protagonists in the increases gluconeogenesis of malaria although none of these is directly involved in the process. The paracrine hormones overture seems also a critical but complicated avenue in explaining the increased gluconeogenic activity seen in malaria as there have a close influence

on classical counterregulatory hormones and as well as on themselves. When prostaglandins synthesis, for instance, is inhibited, there is a subsequent rise in glucose production in healthy individuals [126].

In the liver, Kupffer cells the major producer of prostaglandins [117], have high concentrations of the malaria pigment which elicit prostaglandin synthesis, tend towards hyperplastic production of the inflammatory mediators synthesis [127] in subjects with severe malaria [128]. This impairment of Kupffer cell function brings about the concomitant intrahepatic autoregulation loss of the glucose homeostasis. The severity of Kupffer cells dysfunctionality will determine the degree of disturbances in gluconeogenesis. Maximum stimulation of gluconeogenesis is invariably inhibited by intrahepatic factors in uncomplicated malaria cases. As a result, changes in the rate of gluconeogenesis become paramount in chronic adaptation to glucose demand while glycogenosis rates carter for adaptations to acute changes in glucose utilisation of developmental trophozoite stages.

Gluconeogenesis is much more stimulated in cerebral malaria as compared to non-complicated malaria. Therefore, the Kupffer cell-liver parenchymal cell interaction functions at a dual level comprising of an acute stage for emergency situations which regulates the glycogen content while the chronic level monitors gluconeogenesis. The glucose homeostasis regulating hormones respond to the either the acute effects, i.e. insulin, glucagon catecholamines, or the chronically following a delay, i.e. cortisol and growth hormone. With these hormonal controls, the duality of acute-chronic effects within the Kupffer cell-hepatocyte interactions are under the influence of wider and complex products that are produced by both cell types. In essence the hormonal interactions in the Kupffer cell influences the closely related functions in the hepatocyte and vice versa.

The synthesis of glucose by the liver involves the delivery of substrates and a gluconeogenesis pathway that is intact and functional. Gluconeogenesis may be selectively impaired by alanine supply to the liver. In severe malaria, decreased blood flow to the liver [129] as well as hepatocyte dysfunction [130] may play a role in the impairment of alanine delivery to the liver consequently affecting gluconeogenesis [119]. There is a difference in the ability of reduced alanine supply to the liver in influencing gluconeogenesis that is not experienced with glycerol or glutamine [21]. This is mainly due to two of many possible causes, one which is physiological and another analytical. Glutamine and glycerol are converted to glucose may occur in the liver and the kidney as well while glucose synthesis from alanine is mainly confined to the liver. Furthermore, the measurement of glucose metabolism using stable isotopes does not discriminate hepatic and kidney gluconeogenesis [123]. Regardless, the complexity of these interactions is further intricated by the endocrinological function of the adipose tissue and its influence on both liver and muscle cell types but the increase in gluconeogenesis in malaria remains a fundamental fact.

9. Free fatty acids (FFAs) in malarial glucose regulation

While data in literature about FFAs in malaria seem conflicting, elevated plasma concentration of FFAs and triacylglycerols have been reported in acute malaria amongst adult subjects [131, 132] and in children too [128]. However, evidence exists on the absence of change in

plasma concentrations of FFAs over prolonged fast in malaria patients [133]. Actually, in vitro data has shown a stimulation of lipogenesis and inhibition of lipolysis by malaria products [134]. In normal human beings an increase in glucose concentration has a tendency to suppress adipocytes lipolysis [135]. However, it is still not clear whether an increase of glucose in malaria will have the same effect. There has been a constant finding that high-density and low-density lipoproteins were lower in malaria cases as compared to controls and triacylglycerols were higher as compared to normal controls but without statistical significance when compared to controls displaying some symptoms e.g. fibrillations [135]. In acute malaria, plasma glucose has been shown to remain significantly elevated even when plasma FFAs are no longer increased [132]. Hepatic autoregulation is defined by an acute increase in FFAs which stimulates gluconeogenesis, to replenish depleted glycolysis intermediates, [136] and decrease glycogenesis [137, 138] with glucose production remaining the same [136, 138–140]. Hepatic autoregulation of glucose metabolism is attributed to both intrahepatic and extrahepatic. Ultimately, the autoregulatory mechanism rest on the decrease of liver glycogenolysis facilitated by insulin secretion to counteract FFAs stimulatory effects on glucose production during fasting. Hepatic glycogen content plays a regulatory role in glycogenolysis such that in malaria, where there is a low glycogen content, it is expected that there is no effect of FFAs on extrahepatic regulation [141].

10. Malaria treatment and glucose metabolism

Paroxysms of fever are usually the classical presentation of *P. falciparum* induced malaria. The febrile paroxysms are generally associated with shaking chills, profuse sweating, headache, rigours, fatigue, arthralgia, back ache, abdominal pain, nausea with vomiting, diarrhoea and at times prehepatic jaundice [142]. Atypical manifestations of malaria are more common as most classical symptoms are observed in a section of the malaria infected individuals (50–70%). In severe cases of malaria (SM) patients may present with cerebral malaria (CM), cerebellar ataxia or multiple seizures, hypoglycaemic seizures, cerebral malaria, acute kidney injury, severe malaria anaemia (SMA), thrombocytopaenia, haemoglobinuria, noncardiogenic pulmonary oedema, acute respiratory disease syndrome/ acute respiratory lung injury and other related conditions [143]. Hyperglycaemia is also a prominent finding, although usually missed, in malaria through increased glucose production and possibly insulin resistance driven by the proinflammatory mediatory common in malaria [144]. The hyperglycaemia may invariably lead to non-ketotic hyperosmolar hyperglycaemia state shock with higher fatal outcomes as compared to normoglycaemic individuals [26]. Therefore, treatment should be aimed at alleviating these manifestations more in malaria as well as the parasite. However, major treatment regimens are anti-parasitic than they are anti-disease. An association of hyperglycaemia, severe malaria and CM has been observed to have more fatal outcomes as there is a high glucose production stimulation [145]. However, the hyperglycaemic cases have been staccato in nature with reports of one or two cases out of many cases [146].

Various anti-malarial agents have been used for the treatment of malaria with some having negative effect on glucose homeostasis. These include the use hydroxychloroquine, hydroquinolones, artemisinin and its derivatives. Experimental malaria treatment has been reported with a range of phytochemicals coming into use which showed preservation of glucose

homeostasis bearing in mind that some of the phototherapeutics have anti-inflammatory activities that may influences insulin resistance of malaria [147]. The effect of quinine and other quinolones on hypoglycaemia has been reported by many investigators and will not be covered here. The use of asiatic acid and other triterpenes is an area that is emerging in the fight against malaria. Glucose homeostasis during administration of the phytochemicals in malaria is given below:

10.1. Asiatic acid (AA) and glucose homeostasis in malaria

In streptozotocin (STZ)-induced diabetic rats, AA has been shown to have an anti-diabetic effect where it mediates glycogenolysis and release of glucose for glycolysis [148]. Hypoglycaemia development in malaria has been attributed to anti-malarial agents like quinine and hydroxychloroquine which displays hyperinsulinemia effects [149]. The triad of hypoglycaemia, hyperlactaemia and non-respiratory acidosis (nRA) are associated with elevated concomitantly in diseases that are not associated with malaria and AA has been shown to alleviate such conditions through inhibition of pro-inflammatory mediators like TNF-α [150]. The causal relationship that exists between deranged glucose homeostasis and malaria is linked through TNF-α [151]. Even in diseases such as *Borrelia recurrentis*, the triumvirate of hypoglycaemia, nRA and hyperlactaemia is present showing that the inflammatory response is involved [152]. AA has both an anti-parasitic and anti-disease effect in malaria [5, 8, 9, 13]. It has been shown that AA influences glucose metabolism and this could be through its effect on the inhibition of soluble inflammatory mediators such TNF-α [8]. Associated with this glucose homeostasis attenuation by AA was also an observable effect of the phytochemical on the hormonal milieu in malaria [8]. Together with an anti-parasitic activity, AA has anti-hyperglycaemic, antioxidant, pro-oxidant properties that are essential for glucose metabolism and has been shown to attenuate key glycolytic enzymes in diabetes mellitus as well as in murine malaria [8, 153].

On the hormonal modulation aspect, AA influences glucagon effects on food and water intake and weight in that it terminates the satiate and anorexic effect of the hormone when in high concentrations as in malaria [154]. AA oral administration has also been shown to ablate hyperlactaemia, which is a product of malaria induced-hypoxia, resulting in the wellbeing of the experimental animals not seen in the malaria infected non-treated animals [155].

The carbohydrate metabolic influence and anti-inflammatory effect of AA has been observed and this makes the phytopharmaceutical's ability to attenuate nRA, hyperlactatemia and hypoglycaemia in malaria possible [8]. The transient and fatal hyperglycaemia observed in end-stage malaria and driven by inflammation-induced insulin resistance may be ameliorated by the administration of AA through its anti-hyperglycaemic and immunologic effect.

11. Conclusion

Malaria syndrome vacillates between different events occurring concurrently or in episodes of dissimilar presentations of which glucose homeostatic dysfunction is a prominent one. Hypoglycaemia is driven by an increased consumption of energy which causes the activation

of GLUT1 glucose transporters causing increased glucose uptake into both the infected and uninfected cell. PfHT supplies glucose to growing parasite exacerbating hypoglycaemia. Hyperglycaemia, hypoglycaemia, hyperlactaemia and hyperinsulinemia are facets of the syndrome in contention for supremacy in malaria which other forms of malarial treatment tend to promote. Asiatic acid and other similar phytochemical with known pleiotropic effects promise to provide anti-parasitic and anti-disease effect in malaria.

Conflict of interest

Authors declare no conflict of interest.

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References

[1] D'Alessandro U, Ubben D, Hamed K, Ceesay SJ, Okebe J, Taal M, et al. Malaria in infants aged less than six months-Is it an area of unmet medical need? Malaria Journal. 2012;**11**:400. Available from: http://www.malariajournal.com/content/11/1/400

[2] Doolan DL, Dobañ C, Baird JK. Acquired immunity to malaria. Clinical Microbiology Reviews. 2009;**22**(1):13-36. DOI: 10.1128/CMR.00025-08

[3] WHO. Severe falciparum malaria. Communicable diseases cluster. Transactions of the Royal Society of Tropical Medicine and Hygiene. 2000;**94**:1-90

[4] Cox J, Hay SI, Abeku TA, Checchi F, Snow RW. The uncertain burden of *Plasmodium falciparum* epidemics in Africa. Trends in Parasitology. 2007;**23**:142-148

[5] Mavondo GA, Mkhwananzi BN, Mabandla MV, Musabayane CT. Asiatic acid influences parasitaemia reduction and ameliorates malaria anaemia in *P. berghei* infected Sprague-Dawley male rats. BMC Complementary and Alternative Medicine. 2016;**16**(1):357. DOI: 10.1186/s12906-016-1338-z

[6] Agbenyega T, Angus BJ, Bedu-Addo G, Baffoe-Bonnie B, Guyton T, Stacpoole PW, et al. Glucose and lactate kinetics in children with severe malaria. The Journal of Clinical Endocrinology and Metabolism. 2000;**85**:1569-1576

[7] Binh TQ, Davis TM, Johnston W, Thu LT, Boston R, Danh PT, et al. Glucose metabolism in severe malaria: Minimal model analysis of the intravenous glucose tolerance test incorporating a stable glucose label. Metabolism. 1997;**46**:1435-1440

[8] Mavondo GA, Mkhwananzi BN, Mabandla MV, Musabayane CT. Asiatic acid influences glucose homeostasis in *P. berghei* murine malaria infected Sprague Dawley rats. African Journal of Traditional, Complementary, and Alternative Medicines. 2016;**13**(5):91-101. DOI: 10.21010/ajtcam.v13i5.13

[9] Mavondo GA, Musabayane CT. Transdermal drug delivery of asiatic acid influences renal function and electrolyte handling in *Plasmodium berghei*-infected Sprague-Dawley male rats. Journal of Diseases and Medicinal Plants. 2018;**4**(1):18-29. DOI: 10.11648/j.jdmp.20180401.13

[10] Mavondo GA. Malaria disease perspective and an opinion: Should malaria treatment target the parasite or the malarial pathophysiology generated by the parasite or both? EC Microbiology. 2017;**7**(5):149-154

[11] Davis TM, Binh TQ, Thu le TA, Long TT, Johnston W, Robertson K, et al. Glucose and lactate turnover in adults with *falciparum* malaria: Effect of complications and antimalarial therapy. Transactions of the Royal Society of Tropical Medicine and Hygiene. 2002;**96**:411-417

[12] Mavondo GA, Kasvosve I. Antimalarial phytochemicals: Delineation of the triterpene asiatic acid malarial anti-disease and pathophysiological remedial activities-part II. Journal of Infectious Disease and Pathology. 2017;**1**:103

[13] Mavondo GA, Kasvosve I. Antimalarial phytochemicals: Delineation of the triterpene asiatic acid malarial anti-disease and pathophysiological remedial activities-part I. Journal of Infectious Disease and Pathology. 2017;**1**:104

[14] Mavondo GA, Musabayane CT. Asiatic acid-pectin hydrogel matrix patch transdermal delivery system influences parasitaemia suppression and inflammation reduction in *P. berghei* murine malaria infected Sprague-Dawley rats. Asian Pacific Journal of Tropical Medicine. 2016;**9**(12):1172-1180. DOI: 10.1016/j.apjtm.2016.10.008

[15] Eltahir EM, ElGhazali1 G, A-Elgadir TME, A-Elbasit IE, Elbashir MI, Giha1 HA. Raised plasma insulin level and homeostasis model assessment (HOMA) score in cerebral malaria: Evidence for insulin resistance and marker of virulence. Acta Biochimica Polonica. 2010;**57**(4):513-520

[16] English M, Sauerwein R, Waruiru C, Mosobo M, Obiero J, Lowe B, et al. Acidosis in severe childhood malaria. The Quarterly Journal of Medicine. 1997;**90**:263-270

[17] Maier AG, Rug M, O'Neill MT, Brown M, Chakravorty S, Szestak T, et al. Exported proteins required for virulence and rigidity of *Plasmodium falciparum*-infected human erythrocytes. Cell. 2008;**134**:48-61

[18] Maier AG, Cooke BM, Cowman AF, Tilley L. Malaria parasite proteins that remodel the host erythrocyte. Nature Reviews. 2009;**7**:341-354

[19] Moxon CA, Grau GE, Craig AG. Malaria: Modification of the red blood cell and consequences in the human host. British Journal of Haematology. 2011;**154**:670-679. DOI: 0.1111/j.1365-2141.2011.08755.x

[20] Cowman AF, Crabb BS. Invasion of red blood cells by malaria parasites. Cell. 2006;**124**:755-766. DOI: 10.1016/j.cell.2006.02.006

[21] Dekker E, Hellerstein M, Romijn JA, Neese RA, Peshu N, Endert E, et al. Glucose homeostasis in children with *Falciparum* malaria: Precursor supply limits gluconeogenesis and glucose production. Journal of Clinical Endocrinology and Metabolism. 1997;**82**(8): 2514-1521. DOI: 10.1210/jc.82.8.2514

[22] Krishna S, Woodrow CJ, Burchmore RJ, Saliba KJ, Kirk K. Hexose transport in asexual stages of *Plasmodium falciparum* and kinetoplastidae. Parasitology Today. 2000;**16**:516-521

[23] Woodrow CJ, Burchmore RJ, Krishna S. Hexose permeation pathways in *Plasmodium falciparum*-infected erythrocytes. Proceedings of the National Academy of Sciences of the United States of America. 2000;**29**:9931-9936

[24] Kirk K, Horner HA, Kirk J. Glucose uptake in *Plasmodium falciparum*-infected erythrocytes is an equilibrative not an active process. Molecular and Biochemical Parasitology. 1996;**82**:195-205

[25] Giha HA, Elghazali G, A-Elgadir TM, A-Elbasit IE, Eltahir EM, Baraka OZ, et al. Clinical pattern of severe *Plasmodium falciparum* malaria in Sudan in an area characterized by seasonal and unstable malaria transmissio. Transactions of the Royal Society of Tropical Medicine and Hygiene. 2005;**99**:243-251

[26] Osier FH, Berkley JA, Ross A, Sanderson F, Mohammed S, Newton CR. Abnormal blood glucose concentrations on admission to a rural Kenyan district hospital: Prevalence and outcome. Archives of Disease in Childhood. 2003;**88**:621-625

[27] Wood IS, Trayhurn P. Glucose transporters (GLUT and SGLT): Expanded families of sugar transport proteins. The British Journal of Nutrition. 2003;**89**(7):3-9

[28] Hruz PW, Mueckler MM. Structural analysis of the GLUT1 facilitative glucose transporter (review). Molecular Membrane Biology. 2001;**18**:183-193

[29] Tsirigos KD, Peters C, Shu N, Käll L, Elofsson AT. The TOPCONS web server for consensus prediction of membrane protein topology and signal peptides. Nucleic Acids Research. 2015;**43**:W401-W407

[30] Stuart CA, Wen G, Gustafson WC, Thompson EA. Comparison of GLUT1, GLUT3, and GLUT4 mRNA and the subcellular distribution of their proteins in normal human muscle. Metabolism. 2000;**49**:1604-1609

[31] Stuart CA, Yin D, Howell ME, Dykes RJ, Laffan JJ, Ferrando AA. Hexose transporter mRNAs for GLUT4, GLUT5, and GLUT12 predominate in human muscle. American Journal of Physiology. Endocrinology and Metabolism. 2006;**291**:E1067-E1073

[32] Wood IS, Hunter L, Trayhurn P. Expression of Class III facilitative glucose transporter genes (GLUT-10 and GLUT-12) in mouse and human adipose tissues. Biochemical and Biophysical Research Communications. 2003;**308**:43-49

[33] Bryant NJ, Govers R, James DE. Regulated transport of the glucose transporter GLUT4. Nature Reviews. Molecular Cell Biology. 2002;**3**:267-277

[34] Al-Hasani H, Kunamneni RK, Dawson K, Hinck CS, Muller-Wieland D, Cushman SW. Roles of the N- and C-termini of GLUT4 in endocytosis. Journal of Cell Science. 2002; **115**:131-140

[35] Sandoval IV, Martinez-Arca S, Valdueza J, Palacios S, Holman GD. Distinct reading of different structural determinants modulates the dileucine-mediated transport steps of the lysosomal membrane protein LIMPII and the insulin-sensitive glucose transporter GLUT4. The Journal of Biological Chemistry. 2000;**275**:39874-39885

[36] Martinez-Arca S, Lalioti VS, Sandoval IV. Intracellular targeting and retention of the glucose transporter GLUT4 by the perinuclear storage compartment involves distinct carboxyl-tail motifs. Journal of Cell Science. 2000;**113**:1705-1715

[37] Huang S, Czech MP. The GLUT4 glucose transporter. Cell Metabolism Review. 2007;**5**:237-252

[38] Herman MA, Kahn BB. Glucose transport and sensing in the maintenance of glucose homeostasis and metabolic harmony. The Journal of Clinical Investigation. 2006;**116**: 1767-1775

[39] Rose AJ, Richter EA. Skeletal muscle glucose uptake during exercise: How is it regulated? Physiology (Bethesda). 2005;**20**:260-270

[40] Thong FS, Dugani CB, Klip A. Turning signals on and off: GLUT4 traffic in the insulin-signaling highway. Physiology (Bethesda). 2005;**20**:271-284

[41] Watson RT, Kanzaki M, Pessin JE. Regulated membrane trafficking of the insulin-responsive glucose transporter 4 in adipocytes. Endocrine Reviews. 2004;**25**:177-204

[42] Jiang ZY, Chawla A, Bose A, Way M, Czech MP. A phosphatidylinositol 3-kinase-independent insulin signaling pathway to N-WASP/Arp2/3/F-actin required for GLUT4 glucose transporter recycling. The Journal of Biological Chemistry. 2003;**277**:509-515

[43] Tang X, Powelka AM, Soriano NA, Czech MP, Guilherme A. PTEN, but not SHIP2, suppresses insulin signaling through the phosphatidylinositol 3-kinase/Akt pathway in 3T3–L1 adipocytes. The Journal of Biological Chemistry. 2005;**280**:22523-22529

[44] Gual P, Gonzalez T, Gremeaux T, Barres R, Le Marchand-Brustel Y, Tanti JF. Hyperosmotic stress inhibits insulin receptor substrate-1 function by distinct mechanisms in 3T3–L1 adipocytes. The Journal of Biological Chemistry. 2003;**278**:26550-26557

[45] Sbrissa D, Shisheva A. Acquisition of unprecedented phosphatidylinositol 3, 5-bisphosphate rise in hyperosmotically stressed 3T3–L1 adipocytes, mediated by ArPIKfyve-PIKfyve pathway. The Journal of Biological Chemistry. 2005;**280**:7883-7889

[46] Um SH, D'Alessio D, Thomas G. Nutrient overload, insulin resistance, and ribosomal protein S6 kinase 1, S6K1. Cell Metabolism. 2006;**3**:393-402

[47] Kim JK, Fillmore JJ, Sunshine MJ, Albrecht B, Higashimori T, Kim DW, et al. PKC-theta knockout mice are protected from fat-induced insulin resistance. The Journal of Clinical Investigation. 2004;**114**:823-827

[48] Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante Jr AW. Obesity is associated with macrophage accumulation in adipose tissue. The Journal of Clinical Investigation. 2003;**112**:1796-1808

[49] Ozcan U, Yilmaz E, Ozcan L, Furuhashi M, Vaillancourt E, Smith RO, et al. Chemical chaperones reduce ER stress and restore glucose homeostasis in a mouse model of type 2 diabetes. Science. 2006;**313**:1137-1140

[50] Mueckler M, Thorens B. The SLC2 (GLUT) family of membrane transporters. Molecular Aspects of Medicine. 2013;**34**:121-138

[51] Tal M, Schneider DL, Thorens B, Lodish HF. Restricted expression of the erythroid/brain glucose transporter isoform to perivenous hepatocytes in rats modulation by glucose. The Journal of Clinical Investigation. 1990;**86**:986-992

[52] Meireles P, Sales-Dias J, Andrade CM, Mello-Vieira J, Mancio-Silva L, Simas JP, et al. GLUT1-mediated glucose uptake plays a crucial role during *Plasmodium* hepatic infection. Cellular Microbiology. 2017;**19**(2):e12646

[53] Koranyi L, Bourey RE, James D, Mueckler M, Fiedorek Jr FT, Permutt MA. Glucose transporter gene expression in rat brain: Pretranslational changes associated with chronic insulin-induced hypoglycemia, fasting, and diabetes. Molecular and Cellular Neurosciences. 1991;**2**:244-225

[54] Manel N, Kim FJ, Kinet S, Taylor N, Sitbon M, Battini JL. The ubiquitous glucose transporter GLUT-1 is a receptor for HTLV. Cell. 2003;**115**:449-459

[55] Loisel-Meyer S, Swainson L, Craveiro M, Oburoglu L, Mongellaz C, Costa C. Glut 1-mediated glucose transport regulates HIV infection. Proceedings of the National Academy of Sciences of the United States of America. 2012;**109**:2549-2554

[56] Prudencio M, Rodriguez A, Mota MM. The silent path to thousands of merozoites: The *Plasmodium* liver stage. Nature Reviews. Microbiology. 2006;**4**:849-856

[57] Penkler G, du Toit F, Adams W, Rautenbach M, Palm DC, van Niekerk DD, et al. Construction and validation of a detailed kinetic model of glycolysis in *Plasmodium falciparum*. The FEBS Journal. 2015;**282**:1481-1511

[58] Hellwig B, Joost HG. Differentiation of erythrocyte-(GLUT1), liver-(GLUT2), and adipocyte-type (GLUT4) glucose transporters by binding of the inhibitory ligands cytochalasin B, forskolin, dipyridamole, and isobutylmethylxanthine. Molecular Pharmacology. 1991;**40**:383-389

[59] Joet T, Eckstein-Ludwig U, Morin C, Krishna S. Validation of the hexose transporter of *Plasmodium falciparum* as a novel drug target. Proceedings of the National Academy of Sciences of the United States of America. 2003;**100**:7476-7479

[60] Tjhin ET, Staines HM, van Schalkwyk DA, Krishna S, Saliba KJ. Studies with the *Plasmodium falciparum* hexokinase reveal that PfHT limits the rate of glucose entry into glycolysis. FEBS Letters. 2013;**587**:3182-3187

[61] Slavic K, Delves MJ, Prudencio M, Talman AM, Straschil U, Derbyshire ET. Use of a selective inhibitor to define the chemotherapeutic potential of the plasmodial hexose transporter in different stages of the parasite's life cycle. Antimicrobial Agents and Chemotherapy. 2011;**55**:2824-2830

[62] Slavic K, Straschil U, Reininger L, Doerig C, Morin C, Tewari R, et al. Life cycle studies of the hexose transporter of *Plasmodium* species and genetic validation of their essentiality. Molecular Microbiology. 2010;**75**:1402-1413

[63] Itani S, Torii M, Ishino T. D-Glucose concentration is the key factor facilitating liver stage maturation of *Plasmodium*. Parasitology International. 2014;**63**:584-590

[64] Shrayyef MZ, Gerich JE. Normal glucose homeostasis. In: Poretsky L, editor. Principles of Diabetes Mellitus. Berlin, Germany: Springer; 2010

[65] Ploemen IH, Prudencio M, Douradinha BG, Ramesar J, Fonager J, van Gemert GJ. Visualisation and quantitative analysis of the rodent malaria liver stage by real time imaging. PLoS One. 2009;**4**:e7881

[66] Prudencio M, Rodrigues CD, Ataide R, Mota MM. Dissecting in vitro host cell infection by *Plasmodium* sporozoites using flow cytometry. Cellular Microbiology. 2008;**10**:218-224

[67] Kroemer G, Pouyssegur J. Tumor cellmetabolism: Cancer's Achilles' heel. Cancer Cell. 2008;**13**:472-482

[68] O'Neil RG, Wu L, Mullani N. Uptake of a fluorescent deoxyglucose analog (2-NBDG) in tumor cells. Molecular Imaging and Biology. 2005;**7**:388-392

[69] Yamada K, Saito M, Matsuoka H, Inagaki N. A real-time method of imaging glucose uptake in single, living mammalian cells. Nature Protocols. 2007;**2**:753-762

[70] Cunningham JJ, Gulino MA, Meara PA, Bode HH. Enhanced hepatic insulin sensitivity and peripheral glucose uptake in cold acclimating rats. Endocrinology. 1985; **117**:1585-1589

[71] Pencek RR, James FD, Lacy DB, Jabbour K, Williams PE, Fueger PT, et al. Exercise-induced changes in insulin and glucagon are not required for enhanced hepatic glucose uptake after exercise but influence the fate of glucose within the liver. Diabetes. 2004;**53**:3041-3047

[72] Bitar MS, Al-Saleh E, Al-Mulla F. Oxidative stress-mediated alterations in glucose dynamics in a genetic animal model of type II diabetes. Life Sciences. 2005;**77**:2552-2573

[73] Yu JW, Sun LJ, Liu W, Zhao YH, Kang P, Yan BZ. Hepatitis C virus core protein induces hepatic metabolism disorders through down-regulation of the SIRT1-AMPK signaling pathway. International Journal of Infectious Diseases. 2013;**17**:e539-e545

[74] Blume M, Rodriguez-Contreras D, Landfear S, Fleige T, Soldati-Favre D, Lucius R, et al. Hostderived glucose and its transporter in the obligate intracellular pathogen *Toxoplasma gondii* are dispensable by glutaminolysis. Proceedings of the National Academy of Sciences of the United States of America. 2009;**106**:12998-13003

[75] Kasai D, Adachi T, Deng L, Nagano-Fujii M, Sada K, Ikeda M. HCV replication suppresses cellular glucose uptake through down-regulation of cell surface expression of glucose transporters. Journal of Hepatology. 2009;**50**:883-894

[76] Takanaga H, Chaudhuri B, Frommer WB. GLUT1 and GLUT9 as major contributors to glucose influx in HepG2 cells identified by a high sensitivity intramolecular FRET glucose sensor. Biochimica et Biophysica Acta. 2008;**1778**:1091-1099

[77] Albuquerque SS, Carret C, Grosso AR, Tarun AS, Peng X, Kappe SH. Host cell transcriptional profiling during malaria liver stage infection reveals a coordinated and sequential set of biological events. BMC Genomics. 2009;**10**:270

[78] Blodgett DM, De Zutter JK, Levine KB, Karim P, Carruthers A. Structural basis of GLUT1 inhibition by cytoplasmic ATP. The Journal of General Physiology. 2007;**130**:157-168

[79] Levine KB, Cloherty EK, Fidyk NJ, Carruthers A. Structural and physiologic determinants of human erythrocyte sugar transport regulation by adenosine triphosphate. Biochemistry. 1998;**37**:12221-12232

[80] Cloherty EK, Diamond DL, Heard KS, Carruthers A. Regulation of GLUT1-mediated sugar transport by an antiport/uniport switch mechanism. Biochemistry. 1996;**35**:13231-13239

[81] Thorens B, Cheng ZQ, Brown D, Lodish HF. Liver glucose transporter: A basolateral protein in hepatocytes and intestine and kidney cells. The American Journal of Physiology. 1990;**259**:C279-C285

[82] Karim S, Adams DH, Lalor PF. Hepatic expression and cellular distribution of the glucose transporter family. World Journal of Gastroenterology. 2012;**18**:6771-6781

[83] Uldry M, Ibberson M, Hosokawa M, Thorens B. GLUT2 is a high affinity glucosamine transporter. FEBS Letters. 2002;**524**:199-203

[84] Bilir BM, Gong TW, Kwasiborski V, Shen CS, Fillmore CS, Berkowitz CM, et al. Novel control of the position-dependent expression of genes in hepatocytes. The GLUT-1 transporter. The Journal of Biological Chemistry. 1993;**268**:19776-19784

[85] Simpson IA, Appel NM, Hokari M, Oki J, Holman GD, Maher F. Blood-brain barrier glucose transporter: Effects of hypo- and hyperglycemia revisited. Journal of Neurochemistry. 1999;**72**:238-247

[86] Ebert BL, Firth JD, Ratcliffe PJ. Hypoxia and mitochondrial inhibitors regulate expression of glucose transporter-1 via distinct Cis-acting sequences. The Journal of Biological Chemistry. 1995;**270**:29083-29089

[87] Ng S, March S, Galstian A, Hanson K, Carvalho T, Mota MM, et al. Hypoxia promotes liver-stage malaria infection in primary human hepatocytes in vitro. Disease Models & Mechanisms. 2014;**7**:215-224

[88] Chen C, Pore N, Behrooz A, Ismail-Beigi F, Maity A. Regulation of glut1 mRNA by hypoxia-inducible factor-1. Interaction between H-ras and hypoxia. The Journal of Biological Chemistry. 2001;**276**:9519-9525

[89] Koseoglu MH, Beigi FI. Mechanism of stimulation of glucose transport in response to inhibition of oxidative phosphorylation: Analysis with myc-tagged Glut1. Molecular and Cellular Biochemistry. 1999;**194**:109-116

[90] Barnes K, Ingram JC, Porras OH, Barros LF, Hudson ER, Fryer LG. Activation of GLUT1 by metabolic and osmotic stress: Potential involvement of AMP-activated protein kinase (AMPK). Journal of Cell Science. 2002;**115**:2433-2442

[91] Egert S, Nguyen N, Schwaiger M. Myocardial glucose transporter GLUT1: Translocation induced by insulin and ischemia. Journal of Molecular and Cellular Cardiology. 1999;**31**:1337-1344

[92] Perrini S, Natalicchio A, Laviola L, Belsanti G, Montrone C, Cignarelli A. Dehydroepiandrosterone stimulates glucose uptake in human and murine adipocytes by inducing GLUT1 and GLUT4 translocation to the plasma membrane. Diabetes. 2004;**53**:41-52

[93] Abliz A, Deng W, Sun R, Guo W, Zhao L, Wang W. Wortmannin, PI3K/Akt signaling pathway inhibitor, attenuates thyroid injury associated with severe acute pancreatitis in rats. International Journal of Clinical and Experimental Pathology. 2015; **8**(11):13821-13833

[94] Lee EE, Ma J, Sacharidou A, Mi W, Salato VK, Nguyen N. A protein kinase C phosphorylation motif in GLUT1 affects glucose transport and is mutated in GLUT1 deficiency syndrome. Molecular and Cellular Biochemistry. 2015;**58**:845-853

[95] Pagliassotti MJ, Cherrington AD. Regulation of net hepatic glucose uptake in vivo. Annual Review of Physiology. 1992;**54**:847-860

[96] Danquah I, Bedu-Addo G, Mockenhaupt FP. Type 2 diabetes mellitus and increased risk for malaria infection. Emerging Infectious Diseases. 2010;**16**:1601-1604

[97] Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: Estimates for the year 2000 and projections for 2030. Diabetes Care. 2004;**27**:1047-1053

[98] Raghunath P. Impact of type 2 diabetes mellitus on the incidence of malaria. Journal of Infection and Public Health. 2017;**10**:357-358. DOI: 10.1016/j.jiph.2016.08.013

[99] Ferguson MAJ, Brimacombe JS, Brown JR, Crossman A, Dix A, Field RA, et al. The GPI biosynthetic pathway as a therapeutic target for African sleeping sickness. Biochimica et Biophysica Acta. 1999;**1455**:327-340

[100] Miller LH, Roberts T, Shahabuddin M, M-C. TF. Analysis of sequence diversity in the *Plasmodium falciparum* merozoite surface protein-1 (MSP-1). Molecular and Biochemical Parasitology. 1993;**59**:1-14

[101] Naik RS, Davidson EA, Gowda DC. Developmental stage-specific biosynthesis of glycosylphosphatidylinositol anchors in intraerythrocytic *Plasmodium falciparum* and its inhibition in a novel manner by mannosamine. The Journal of Biological Chemistry. 2000;**275**:24506-24511

[102] Schofield L, Hackett F. Signal transduction in host cells by a glycosylphosphatidylinositol toxin of malaria parasites. The Journal of Experimental Medicine. 1993;**1**(1):145-153

[103] Naik RS, Branch OH, Woods AS, Vijaykumar M, Perkins GJ, Nahlen BL, et al. Glycosylphosphatidylinositol anchors of *Plasmodium falciparum*: Molecular characterization and naturally elicited antibody response that may provide immunity to malaria pathogenesis. Journal of Experimental Medicine. 2000;**192**(11):1563-1575

[104] Gowda DC. Structure and activity of glycosylphosphatidylinositol anchors of *Plasmodium falciparum*. Clinical Microbiology and Infection. 2002;**9**:983-990

[105] Taylor K, Bate CAW, Carr RE, Butcher GA, Taverne J, Playfair JHL. Phospholipid-containing toxic malaria antigens induce hypoglycaemia. Clinical and Experimental Immunology. 1992;**90**:1-5

[106] Caro HN, Sheikh NA, Taverne J, Playfair JHL, Rademacher TW. Structural similarities among malaria toxins, insulin second messengers, and bacterial endotoxin. Infection and Immunity. 1996;**64**(8):3438-3441 0019-9567/96/$04.0010

[107] Saliba KJ, Kirk K. pH regulation in the intracellular malaria parasite, *Plasmodium falciparum*. H(+) extrusion via a v-type h(+)-atpase. The Journal of Biological Chemistry. 1999;**274**:33213-33219

[108] Allen RJ, Kirk K. The membrane potential of the intraerythrocytic malaria parasite *Plasmodium falciparum*. The Journal of Biological Chemistry. 2004;**279**:11264-11272

[109] Slavic K, Krishna S, Derbyshire ET, Staines HM. Plasmodial sugar transporters as anti-malarial drug targets and comparisons with other protozoa. Malaria Journal. 2011;**10**:165

[110] Olszewski KL, Mather MW, Morrisey JM, Garcia BA, Vaidya AB, Rabinowitz JD, et al. Branched tricarboxylic acid metabolism in *Plasmodium falciparum*. Nature. 2010;**466**:774-778

[111] Manolescu AR, Witkowska K, Kinnaird A, Cessford T, Cheeseman C. Facilitated hexose transporters: New perspectives on form and function. Physiology (Bethesda). 2007;**22**:234-240

[112] Desai SA, Rosenberg RL. Pore size of the malaria parasite's nutrient channel. Proceedings of the National Academy of Sciences of the United States of America. 1997;**94**:2045-2049

[113] Woodrow CJ, Penny JI, Krishna S. Intraerythrocytic *Plasmodium falciparum* expresses a high affinity facilitative hexose transporter. The Journal of Biological Chemistry. 1999;**274**:7272-7277

[114] Kirk K, Horner HA, Elford BC, Ellory JC, Newbold CI. Transport of diverse substrates into malaria-infected erythrocytes via a pathway showing functional characteristics of a chloride channel. The Journal of Biological Chemistry. 1994;**269**:3339-3347

[115] Davis TM, Looareesuwan S, Pukrittayakamee S, Levy JC, Nagachinta B, White NJ. Glucose turnover in severe *falciparumm* malaria. Metabolism: Clinical and Experimental. 1993;**42**:334-340

[116] Kern P, Hemmer CJ, Van Damme J, Gruss HJ, Dietrich M. Elevated tumor necrosis factor alpha and interleukin-6 serum levels as markers for complicated *Plasmodium falciparum* malaria. The American Journal of Medicine. 1989;**87**:139-143

[117] Corssmit EP, Romijn JA, Sauerwein HP. Regulation of glucose production with special attention to nonclassical regulatoryy mechanisms: A review. Metabolism. 2001;**50**:742-755

[118] Newton CRJC, Krishna S. Severe *falciparum* malaria in children: Current understanding of pathophysiology and supportive treatment. Pharmacology Therapeutics. 1998;**79**:1-53

[119] Pukrittayakamee S, Krishna S, Ter Kuile F, Wilaiwan O, Williamson DH, White NJ. Alanine metabolism in acute falciparumm malaria. Tropical Medicine & International Health. 2002;**7**:911-918

[120] White NJ, Warrell DA, Chanthavanich P. Severe hypoglycemia and hyperinsulinemia in *falciparum* malaria. The New England Journal of Medicine. 1983;**309**:61-66

[121] White NJ, Miller KD, Marsh K. Hypoglycaemia in African children with severe malaria. Lancet. 1987;**1**:708-711

[122] Taylor TE, Molyneux ME, Wirima JJ, Alex Fletcher K, Morris K. Blood glucose levels in Malawian children beforee and during the administration of intravenous quinine for severe *falciparum* malaria. The New England Journal of Medicine. 1988;**319**:1040-1047

[123] Stumvoll M, Perriello G, Meyer C, Gerich J. Role of glutamine in human carbohydrate metabolism in kidney and otherr tissues. Kidney International. 1999;**55**:778-792

[124] Cowan G, Planche T, Agbenyega T. Plasma glutamine levels and falciparum malaria. Transactions of the Royal Society of Tropical Medicine and Hygiene. 1999;**93**:616-618

[125] Pukrittayakamee S, White NJ, Davis TM. Glycerol metabolism in severe *falciparum* malaria. Metabolism. 1994;**43**:887-892

[126] Corssmit EP, Romijn JA, Endert E, Sauerwein HP. Indomethacin stimulates basal glucose production in humans without changes in concentrations of glucoregulatory hormones. Clinical Science (Colch). 1993;**85**:679-685

[127] Keller CC, Davenport GC, Dickman KR, Hittner JB, Kaplan SS, Weinberg JB, et al. Suppression of prostaglandin E2 by malaria parasite products and antipyretics promotes overproduction of tumor necrosis factor-a association with the pathogenesis of childhood malarial anemia. The Journal of Infectious Diseases. 2006;**193**:1384-1393

[128] WHO. Communicable Diseases Cluster. Severe *falciparum* malaria. Transactions of the Royal Society of Tropical Medicine and Hygiene. 2000;**94**(Suppl 1):S1-90. PMID: 11103309

[129] Pukrittayakamee S, White NJ, Davis TM. Hepatic blood flow and metabolism in severe *falciparum* malaria: Clearance of intravenously administered galactose. Clinical Science (Colch). 1992;**82**:63-70

[130] Molyneux ME, Looareesuwan S, Menzies IS. Reduced hepatic blood flow and intestinal malabsorption in severe *falciparum* malaria. The American Journal of Tropical Medicine and Hygiene. 1989;**40**:470-476

[131] Onongbu IC, Onyeneke EC. Plasma lipid changes in human malaria. Annals of Tropical Medicine and Parasitology. 1983;**34**:193-196

[132] Davis TME, Pukrittayakamee S, Supanaranond W. Glucose metabolism in quinine-treated patients with uncomplicatedd *falciparum* malaria. Clinical Endocrinology. 1990;**33**:739-749

[133] Kawo NG, Msengi AE, Swai AB, Chuwa LM, Alberti KG, McLarty DG. Specificity of hypoglycaemia for cerebral malariaa in children. Lancet. 1990;**336**:454-547

[134] Taylor K, Carr R, Playfair JH, Saggerson ED. Malarial toxic antigens synergistically enhance insulin signalling. FFSS Letters. 1992;**311**:23M

[135] Visser BJ, Wieten RW, Nagel IM, Grobusch MP. Serum lipids and lipoproteins in malaria-A systematic review and meta-analysis. Malaria Journal. 2013;**12**:442

[136] Chu C, Sherck SM, K I. Effects of free fatty acids on hepatic glycogenosis and gluconeogenesis in consciouss dogs. American Journal of Physiology. Endocrinology and Metabolism. 2002;**282**:E402-E411

[137] Stingl H, Krssak M, M K. Lipid-dependent control of hepatic glycogen stores in healthy humans. Diabetologia. 2001;**44**:48-54

[138] Boden G, Chen X, Capulong E, Mozzoli M. Effects of free fatty acids on gluconeogenesis and autoregulation of glucosee production in type 2 diabetes. Diabetes. 2001;**50**:810-816

[139] Roden M, Stingl H, Chandramouli V e a. Effects of free fatty acid elevation on postabsorptive endogenous glucosee production and gluconeogenesis in humans. Diabetes. 2000;**49**:701-707

[140] Clore JN, Glickman PS, Nestler JE, Blackard WG. In vivo evidence for hepatic autoregulation during FFA stimulated gluconeogenesis in normal humans. The American Journal of Physiology. 1991;**261**:E425-E429

[141] Lam TKT, Carpentier A, Lewis GF, Werve G, Fantus IG, Giacca A. Mechanisms of the free fatty acid-induced increase in hepatic glucose production. American Journal of Physiology. Endocrinology and Metabolism. 2003;**284**:E863-E873

[142] Taylor SM, Molyneux ME, Simel DL, Meshnick SR, Juliano JJ. Does this patient have malaria? Journal of the American Medical Association. 2010;**304**(18):2048-2056

[143] Chianura L, Errante IC, Travi G, Rossotti R, Puoti M. Hyperglycemia in severe falciparum malaria: A case report. Case Reports in Critical Care (Hindawi Publish Corp). 2012;**2012**:3. DOI: 10.1155/2012/312458

[144] Zaki SA, Shanbag P. Atypical manifestations of malaria. Research and Reports in Tropical Medicine. 2011;**2**:9-22

[145] van Thien H, Ackermans MT, Dekker E. Glucose production and gluconeogenesis in adults with cerebral malaria. QJM: An International Journal of Medicine. 2001;**94**(12):709-715

[146] Dass R, Barman H, Duwarah SG, Deka NM, Jain P, Choudhury V. Unusual presentations of malaria in children: An experience from a tertiary care centre in North East India. Indian Journal of Pediatrics. 2010;**77**(6):655-660

[147] Clark IA, Budd AC, Alleva LM, Cowden WB. Human malarial disease: A consequence of inflammatory cytokine release. Malaria Journal. 2006;**5**:85. DOI: 10.1186/1475-2875-5-85

[148] Ramachandran V, Saravanan R. Efcacy of asiatic acid, a pentacyclic triterpene on attenuating the key enzymes activities of carbohydrate metabolism in streptozotoc ininduced diabetic rats. Phytomedicine. 2013;**20**:230-236

[149] Asamoah KA, Robb DA, Furman BL. Chronic chloroquine treatment enhances insulin release in rats. Diabetes Research and Clinical Practice. 1990;**9**:273-278

[150] Baker RG, Hayden MS. NF-kB, infammation, and metabolic disease. Cell Metabolism. 2011;**15**:11-22

[151] Grau GE, Fajardo LF, Piquet P-F, Allet B, Lambert P-H. Tumor necrosis factor (cachectin) as an essential mediator in murine cerebral malaria. Science. 1987;**237**:1210-1212

[152] Coxon RE, Fekade D, Knox K, Hussein K, Melka A. The efect of antibody against TNF alpha on cytokine response in Jarisch-Herxheimer reactions of louse-borne relapsing fever. The Quarterly Journal of Medicine. 1997;**90**:213-221

[153] Ramachandran V, Saravanan R, Senthilraja P. Antidiabetic and antihyperlipidemic activity of asiatic acid in diabetic rats, role of HMG CoA: In vivo and in silico approaches. Phytomedicine. 2014;**21**:225-232

[154] Chulman JL, Carleton JL, Whitney G, Whitehorn JC. Efect of glucagon on food intake and body weight in man. Journal of Applied Physiology. 1975;**11**:419-421

[155] Dabadghao VS, Singh VB, Sharma D, Meena BL. A study of serum lactate level in malaria and its correlation with severity of disease. International Journal of Advanced Medical and Health Research. 2015;**2**:28-32