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LINKING MALARIA TO TYPE 2 DIABETES MELLITUS: A REVIEW

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Abstract

Malaria and diabetes continue to affect millions of people globally. Although global malaria burden is declining gradually, that of diabetes seems to be increasing. Sub-Saharan Africa with the greatest burden of malaria is predicted to house the greatest proportion of incidence of diabetes by 2030. This prediction though hinges on expected increase in prevalence of obesity, the possible impact of infection in general and Plasmodium infection in particular cannot be overlooked. This review focuses on the effect of Plasmodium infection on circulating glucose level in humans and discusses possible mechanisms by which malaria could be linked to the pathogenesis of type 2 diabetes mellitus (T2DM). Malaria causes inflammation and oxidative stress which could lead to insulin resistance and eventually impact negatively on glucose homeostasis. The nature of malaria-induced inflammation and oxidative stress appears similar to that observed in diabetes and obesity. At the pharmacological level, anti-malarials and anti-diabetics can be synthesized from a common 'biguanides' with possible cross reactivities. At the molecular level, artimisins, a potent class of antimalarials, appear to have capability to transform α-cells in the islets into insulin-secreting β-cells through enhanced gamma amino-butyric acid (GABA) signaling, to improve glucose homeostasis in different models of mammalian cells. Putting together, these various levels of evidence suggest a greater potential for a link between malaria and diabetes. However, more research work is needed for improved understanding of the mechanistic link of malaria to T2DM to properly define the contribution of malaria to the predicted increase in incidence of T2DM in malaria-endemic regions.

Introduction

Glucose is an essential energy source for both humans and malaria parasites. In humans, the rise in glucose level in blood after meals is controlled by absorption into tissues for further metabolic activities. The absorptive process is complex involving different mechanisms that depend on insulin or not. Glucose is hydrophilic and cannot diffuse readily across the lipid bilayer of cell membranes without specific transporter proteins (Mueckler, 1990). Two main types of transporter protein families have been reported for glucose and other sugars (Bouche et al., 2004) depending on the mechanism employed in the transport process. The GLUT family of glucose transporters which facilitates glucose diffusion into cells in an energy and sodium independent manner has 14 isoforms (Mueckler and Thorens, 2013). Glucose transport by the GLUT transporters follows the Michaelis-Menton kinetics (Gottesman et al., 1984) of enzyme-substrate interaction to transport glucose along its concentration gradient from blood into cells. The other family of glucose transporters is the sodium-glucose linked transporter (SGLT) family which facilitates glucose uptake into cells by active transport mechanism against the concentration gradient of glucose. The various isoforms of glucose transporter families differ in tissue-specific expression pattern, sub-cellular localization and substrate kinetics (Gottesman et al., 1984; Mueckler and Thorens, 2013). Although most of the isoforms of glucose transporter proteins do not depend on insulin to transport glucose into cells, failure of cells to respond to insulin-mediated glucose transport is critical in the development of diabetes. This implies that insulin-mediated glucose transport is critical for maintenance of circulating glucose level within the normal range. The transporter protein which depends on insulin is the GLUT 4 and is present in adipose tissue, heart, skeletal muscle and the brain (Abel et al., 2001; Bryant et al., 2002; Katz et al., 1995; Rayner et al., 1994). GLUT4, when synthesized, are stored in specialized vesicles located in the intracellular compartment. Upon the release of insulin due to elevated glucose level as is normally the case after a carbohydrate meal, vesicles containing GLUT4 get translocated from the intracellular compartment to the plasma membrane (Bryant et al., 2002; Shepherd and Kahn, 1999), increasing the number of GLUT4 molecules at the plasma membrane and the subsequent increased transport of glucose by 10–20 folds (Bryant et al., 2002; Shepherd and Kahn, 1999). It is therefore not surprising that impaired translocation and expression of GLUT4 is associated with insulin resistance-mediated pathogenesis of type 2 diabetes mellitus (T2DM) (Garvey et al., 1998; Zierath et al., 1996). Interestingly, GLUT4 expression level is modulated by dietary components (Hajiaghaalipour et al., 2015), exercise (Lehnen et al., 2012) and viral infection (Yu et al., 2011). This review focuses on the effect of *Plasmodium* infection on circulating glucose level in humans and its implication for the development of T2DM.

Infection and Circulating Blood Glucose Level

The role of infection in the regulation of blood glucose is complex. The exact effect depends on the infectious agent, the extent of the infection, the immune status as well as the immune response to the infectious agent. Whereas the presence of some infectious agents such as the *Plasmodia* are independently associated with raised glucose level through insulin resistance (Acquah et al., 2014; Coppieters et al., 2012; Eltahir et al., 2010), helminth infection is rather protective against diabetes (Zaccone and Cooke, 2011). The protection of human host against chronic blood glucose elevation as observed in diabetes, by helminths infection, has been comprehensively demonstrated in both types 1 and 2 diabetes mellitus (Wammes et al., 2014; Wiria et al., 2014; Zaccone and Cooke, 2011) and linked to their immunomodulatory effects (Wiria et al., 2012). The identified effects include induction of T2 helper cells and other regulatory immune cells, suppressed inflammation and improved insulin sensitivity (van Riet et al., 2007; Wiria et al., 2014). Although the burden of heminths infestation is undoubtedly greater in developing countries, the incidence of predicted diabetes is higher in developing than developed countries (IDF, 2015), suggesting a possible attenuation of the helminths-induced protection against diabetes. The attenuated protection could be due to the effects of other parasites such as the *Plasmodium* parasite and viruses that are highly prevalent in developing countries.

Plasmodial Infection, Glucose Level and Insulin Resistance

Despite the observed decline in global malarial cases, the disease still affects millions of people worldwide. In 2016, 216 million cases of malaria were reported globally, with 445,000 deaths (WHO, 2017). Out of this, 194.4 million cases and 407,000 deaths occurred in the African region, making malaria almost an African problem. Malaria is caused by the *Plasmodium* parasite with over 100 species identified to date (White, 2008). Of the numerous species of the parasite identified, only five of them, *P. falciparum*, *P. malariae*, *P. vivax*, *P. ovale* and *P. knowlesi* are known to infect humans (White, 2008). These human host parasites of malaria have a complex lifecycle which involves the female Anopheles mosquito and the human host (Haldar et al., 2007). In the mosquito, sporozoites are produced which get transferred to the human host upon infective bite. In the human host, the liver is the target of the sporozoites where they develop further into infective merozoites which then infect the red blood cells following release into the blood stream. In the erythrocytes, further multiplication occurs which is responsible for the clinical presentation of malarial disease. Of the five *Plasmodial* species that are responsible for human malaria, *P. falciparum* dominates since it contributes more than 95% of the global malaria burden (Guinovart et al., 2006). Malaria is a multifaceted disease, viewed as the most destructive and widespread parasitic infection in the world (Haldar et al., 2007) with children under five years and pregnant women being the most vulnerable hosts.

With glucose being virtually a universal energy source for all kinds of animals, the *Plasmodium* parasite is no exception as it does not survive when deprived of glucose (Slavic et al., 2011). The dependence of the *Plasmodium* parasite on glucose for survival makes it plausible to expect reduced glucose level in malaria-infected patients compared to controls as normally reported for severe cases of the disease (Ogetii et al., 2010). The reduced glucose level even to the point of clinical hypoglycaemia has been ascribed to factors such as impairment of gluconeogenesis, malnutrition, glucose utilisation by parasite, starvation and hyperinsulinemia (Das et al., 1988; Dekker et al., 1997; Phillips et al., 1993; Roe and Pasvol, 2009; White et al., 1987) although, the coexistence of hyperinsulinemia and hypoglycaemia has been challenged (Taylor et al., 1988; White et al., 1987). The reduced glucose level clearly points to the absence of insulin resistance in such instances. In recent times, however, the role of malaria in insulin resistance has been highlighted in human studies. Insulin resistance which refers to the reduced ability of cells to respond to insulin action gives rise to impaired uptake of glucose into cells. Insulin resistance coupled with beta cell dysfunction underpins the development of T2DM. Indeed, in malaria, increased insulin resistance together with reduced secretory function of the beta cells as assessed by the homeostatic models in humans has been reported in adults (Acquah et al., 2014) and children (Eltahir et al., 2010).

Several mechanisms have been reviewed in a comprehensive manner as the means for the development of insulin resistance (Khansari et al., 2009; Lontchi-Yimagou et al., 2013; Muoio and Newgard, 2008; Tilg and Moschen, 2008; Ye, 2013). These include nutritional, hormonal, inflammatory and stress of the endoplasmic reticulum.

The nutritional link to insulin resistance has been via obesity. Indeed, obesity, which signifies malnutrition, is a state of excess energy, stored as fat and is linked to chronic low-grade inflammatory state and associated with insulin resistance (Holland et al., 2011; Wellen and Hotamisligil, 2005). The obesity hypothesis of insulin resistance argues that sustained exposure of tissues to high levels of nutrients gives rise to accumulation of toxic by-products of metabolism which impairs insulin action (Holland et al., 2011; Ye, 2013).This state of positive caloric balance requires favourable genetic and environmental factors to exert the expected negative effects. This may partly explain the concept of obesity paradox (Bouchard et al., 2011; Lavie et al., 2009) in that obese individuals who do not provide the requisite favourable genetic and environmental conditions seem to be rather protected against some negative health effects of obesity (Bouchard et al., 2011).

Interestingly, the obesity paradox that suggests better prognosis for obese/overweight individuals compared with their normal weight counterparts with similar underlying health condition has not been observed in the development of insulin resistance, suggesting that, the concept may be more relevant in the disease state (Lavie et al., 2009). Even in instances where some form of a paradox has been proposed,

it is based on the varied response of the hepatocytes to insulin action whereby enhanced gluconeogenesis, suggestive of insulin resistance, coexists with lipogenesis which signifies normal insulin function (Brown and Goldstein, 2008; Vatner et al., 2015). This kind of selective insulin resistance (Brown and Goldstein, 2008), commonly seen in T2DM, has been ascribed to enhanced substrate availability for hepatic lipogenesis (Vatner et al., 2015) and the effects of other regulatory signals received from various bodily organs (Ferris and Kahn, 2016), especially, the brain (Scherer et al., 2016). As such, the paradox of selective insulin resistance exhibited by the hepatocytes in T2DM (Brown and Goldstein, 2008), is completely different from the obesity paradox (Lavie et al., 2009) since in the case of the former, the selective resistance has not been reported to differ between obese and normal weight individuals. To this end, the role of obesity expressed as adiposity in the development of insulin resistance prior to overt manifestation of T2DM cannot be overlooked. Adipose tissue viewed originally as a passive storage site for triglycerides and cholesterol esters is now considered as a metabolically active group of cells that play varied endocrine roles to influence overall cellular metabolism and immunity (Zhou et al., 2011). As such infection in general and *Plasmodial* infection in particular may have a role in obesity-induced insulin resistance. This view is particularly relevant considering the active endocrine role that the adipose tissue has assumed.

Hormonal Level, Malaria and Diabetes

Several hormones influence blood glucose level. Whereas insulin functions to reduce blood glucose level, a number of other hormones work to rather increase blood glucose level through direct and indirect inhibition of the actions of insulin (Goodyear et al., 1995; Gromada et al., 1997; MacDonald et al., 2007; Pessin and Saltiel, 2000; Vieira et al., 2007). Insulin binds to its receptor, insulin receptor (IR) to activate insulin receptor substrates (IRS1 and IRS2) which subsequently activate phosphatidyl inositol−3 kinase (PI3K) (Goodyear et al., 1995; Pessin and Saltiel, 2000). Eventually, protein kinase B (PKB or AKT) gets activated by PI3K resulting in recruitment and intracellular translocation of GLUT4 to the plasma membrane coupled with the eventual transport of glucose from the blood stream into cells (Goodyear et al., 1995; Jiang et al., 2003; Pessin and Saltiel, 2000). This phosphorylation-dependent signaling system of insulin is required to operate at optimal level to ensure effective glucose transport in an insulin-dependent manner. Under this state, insulin is able to inhibit the action of hormone-sensitive lipase responsible for lipid breakdown to release free fatty acid into circulation (Meyer et al., 1997), suppress glucose release from kidney and liver (Meyer et al., 1998), impair the activity of glucose−6−phosphatase and phosphorylase, which are critical glycogenolytic enzymes (Gerich, 2000), and above all, enhance glucose uptake by muscle and adipose tissue (Øster-Jørgensen et al., 1990).

As such, defective insulin signaling may impair sensitivity of affected cells to the action of insulin (Sesti et al., 2001). Indeed, hyper-phosphorylation of serine residues at positions 302, 307, 612, and 632 of insulin receptor substrate 1 (IRS1) has been observed in rodent models of insulin resistance (Sugita et al., 2004; Um et al., 2004; Yu et al., 2002) and insulin-resistant normal weight individuals whose parents are type 2 diabetic patients (Morino et al., 2005). Interestingly, human cytomegalovirus infection enhances glucose transport through Akt signaling-dependent (Johnson et al., 2001; Kudchodkar et al., 2004) or independent manner (Yu et al., 2011). Reports from studies of human adenovirus 36 (Ad36) infection in rodent models (Krishnapuram et al., 2011; Pasarica et al., 2006) and human cell lines (Krishnapuram et al., 2011; Rogers et al., 2008; Wang et al., 2008) have demonstrated improved glycaemic control through enhanced cellular uptake of glucose in an insulin-independent manner. Ad36 improves glycaemic control by impairing the activation of insulin receptor, IRS1 or IRS2, activating the Ras system to recruit PI3/AKT pathway to lead to the eventual translocation of GLUT4 in abundance and enhanced glucose disposal (Jiang et al., 2010; Krishnapuram et al., 2013). Ras is a known guanine triphosphate-binding protein involved in cell growth and proliferation and an inducer of the PI3K/AKT signaling pathway (Sasaki et al., 2004; Suire et al., 2006). Additionally, the effects of Ras action on glucose transporters are similar to those of insulin (Kozma et al., 1993) but the role of Ras-dependent glucose uptake is only appreciated in impaired insulin signaling (Dorrestijn et al., 1996; Houseknecht et al., 1996). These data suggest that infection with Ad36 may improve glycaemic control in insulin-resistant type 2 diabetic patients and possibly protect non-diabetics against the development of insulin resistance and the development of overt T2DM. It is therefore not surprising to have advocates for the Ras signaling system to be revisited and possibly exploited for therapeutic gains in the fight against T2DM (Krishnapuram et al., 2013). Although such a call is deeply rooted in experimental findings, it may be important to further investigate the Ras-mediated improved glucose disposal system in co-infection settings so as to better understand how multiple parasite interactions in the same host may impact on the Ras signaling system. This is particularly important for developing countries where the double burden of infectious and T2DM are highly prevalent. For instance, a study of the Ras signaling system in appropriate animal models and in humans with co-infection of *Plasmodium* spp. and Ad36 on glucose disposal may contribute to our understanding of the evolution of T2DM in malaria-endemic sub-Saharan Africa. Indeed, malaria is known to cause insulin resistance as assessed by the homeostatic model of insulin resistance (HOMAIR) (Acquah et al., 2014; Coppieters et al., 2012; Eltahir et al., 2010) possibly through inflammation, oxidative stress (Acquah et al., 2016a) and other hormones (Acquah et al., 2017b). However, the specific molecular mechanism(s), employed by *P. falciparum* in inducing the insulin resistance remains to be elucidated. Such information may be critical in our understanding of the

development of T2DM in malaria-endemic regions so as to devise a holistic therapeutic approach to combat the menace. Glucose level is also affected by other hormones such as glucagon, cortisol, growth hormone and catecholeamines. Glucagon is secreted by the α-cells of the islet of Langerhans of the pancreas and its release is mainly triggered by hypoglycaemia but impaired by hyperglycaemia or at glucose concentration lower than that necessary to activate β-cells for insulin release (Gromada et al., 1997; MacDonald et al., 2007; Vieira et al., 2007). The main function of glucagon is catabolic, aimed at reversing the action of insulin, such as activating adenylyl cyclase to enhance glycogen breakdown for glucose release through increased intracellular level of cyclic adenosine monophosphate (cAMP) and stimulation of phosphorylase with resultant rise in glucose level. It is therefore not surprising that dysregulated secretion of glucagon is implicated in the development of diabetes and its associated complications (Quesada et al., 2008). Interestingly, bacterial infection has long been found to influence the action of glucagon (Rocha et al., 1973), although scientific information on the effect of *Plasmodium* infection on glucagon is limited. Cortisol and growth hormone function just like glucagon, to impair the action of insulin by attenuating the inhibitory action of insulin on glucose and fatty acid release. Both hormones induce synthesis of gluconeogenic enzymes and impair glucose transport (De Feo et al., 1989; Rizza et al., 1982). All these hormonal activities which result in raised plasma glucose level may contribute to the development of diabetes if dysregulated. Catecholeamines impair the action and secretion of insulin in a sustained manner to potentiate hyperglycaemic condition through cAMP-dependent activation of glycogenolytic enzymes.

Interestingly, these various counter regulatory hormones to insulin act through different mechanisms synergistically in a manner that, a small rise in their levels, could raise glucose level to heights that cannot be attained by a large rise in level of any one of them (Mitrakou et al., 1991). Considering the various hormones which function to counter the action of insulin in regulating glucose level in the body, it is expected that hyperglycaemia will be a bit more tolerated by the body than hypoglycaemia. It is therefore not surprising that, a lot of people harbor hyperglycaemia for a long time before being diagnosed of diabetes. Indeed, the current estimates of the International Diabetes Federation (IDF) suggest that 193 million people globally live with undiagnosed diabetes mellitus (IDF, 2015). Of these, 156.33 million live in low- and middle-income countries (IDF, 2015). In the sub-Saharan African region, 66.7% of all diabetes cases are undiagnosed due probably to limited resources (IDF, 2015). A situation such as this increases the risk of complications associated with hyperglycaemia.

Malaria and Diabetes Mellitus

Malaria is a disease caused by the *Plasmodium* parasite. Malaria is set to have occurred when a susceptible host of the parasite presents the requisite clinical signs and symptoms of the disease. As such, a mere presence of the parasite in a given host cannot technically connote the presence of the disease. As indicated earlier, the *Plasmodium* parasite is transmitted to the human host by infected female Anopheles mosquitoes upon infective bite of the host by the mosquito. As such, susceptibility to the disease is determined by several host and parasite factors. Type 2 diabetes patients, are known to be more susceptible to malaria and exhibit a higher parasitaemia than non-diabetic controls (Danquah et al., 2010).This finding has been confirmed in a subsequent prospective study where proportionally more diabetics than controls had *P. falciparum* malaria (Acquah et al., 2014). Increased susceptibility to *P. falciparum* infection in diabetics could be an indication of immune weakness of diabetics compared with non-diabetic controls. Indeed, diabetics are known to have impaired immune response to the liver- and/or blood-stage parasites, due probably to waning T cell-dependent immune response (Muller et al., 2005). This allows parasites to grow rapidly in the presence of abundant glucose (Jensen et al., 1983). It is also argued that diabetics may attract more infectious bites from mosquitoes through olfactory signaling system (Takken and Knols, 1999).

Interestingly, a recent study we conducted in rat to investigate the nature of malaria-induced insulin resistance showed that insulin resistance induced by malaria is transient with no significant difference in parasitaemia between diabetic and non-diabetic rats (Acquah et al., 2017b). We also demonstrated that a second episode of *Plasmodium berghei* infection increased insulin resistance to a level similar to the first episode but at a relatively reduced parasitaemia (Acquah et al., 2017b), suggesting a possible immunological priming of affected cells to malaria-induced insulin resistance, probably, through interaction with toll-like receptors which have been found to be important in malaria immunity (Franklin et al., 2009) and nutrient-induced insulin resistance (Senn, 2006).

Toll-like receptors (TLRs) are cell-surface receptors that recognize pathogenic ligands for appropriate innate immune response to be mounted to get rid of detected pathogens. TLRs carry out this immunologic function through the induction of signaling cascades that result in the release of pro-inflammatory cytokines and other oxidative entities necessary for appropriate activation of the adaptive immune system for effective elimination of the contaminating pathogen. The mechanism adopted by the TLRs in fighting pathogenic attacks makes them relevant in several diseases of acute and chronic nature such as malaria and diabetes. In the case of diabetes, the potential for involvement of TLRs in its development can be inferred from reports of ubiquitous expression patterns of TLRs in several tissues including insulin targets (Nishimura and Naito, 2005; Zarember and Godowski, 2002). Additionally, several recent reviews (Dasu et al., 2012; Mudaliar et al., 2014; Sepehri et al., 2016) have highlighted a number of evidence of direct and indirect involvement of

TLRs in the pathogenesis of diabetes. Interestingly, most of the pro-inflammatory cytokines through which TLRs exert their pathogenic diabetogenic activity have been implicated in the clinical presentation of malaria (Mockenhaupt et al., 2006). This finding, which, further highlights the similarity in the pathogenesis of diabetic and malarial conditions calls for the need for further research into the interaction between the two conditions. It is in the light of this that further studies ought to be carried out to explore the possible impact of multiple episodes of *Plasmodium* infection on the development of full-blown T2DM through insulin resistance.

Potential Mechanistic Basis of Malaria-Diabetes Linkage

Inflammation

Malaria being an infectious disease has long been associated with inflammation (Issifou et al., 2003; Kwiatkowski et al., 1990). Indeed inflammation is thought to underpin the clinical signs and symptoms associated with the disease (Clark et al., 2006). Inflammation can be chronic or acute and in the case of malaria, the acute form is more commonly encountered although the chronic form, often observed in asymptomatic state (Bousema et al., 2014; Lindblade et al., 2013; Moxon et al., 2013), is gaining recognition. Indeed, chronic symptomatic malaria infection in rural Zambia was recently reported (Hamainza et al., 2014). Although inflammation is a major host defense mechanism against injury or pathogens such as the *Plasmodium* parasite, the phenomenon can be harmful to the host with resultant acute or chronic pathology if dysregulated. The inflammatory process is mediated by several markers such as selected interleukins (IL), tumor necrosis factor alpha (TNFα), C-reactive protein (CRP) and interferon gamma (IFNγ) (Abdel-Hamid et al., 2013; Bousema et al., 2014; Lindblade et al., 2013; Mbengue et al., 2016; Moxon et al., 2013). The inflammatory process which aims at restoring cellular integrity shares some similarity with haemostasis which targets restoration of vascular integrity after injury. Indeed, both haemostasis and inflammation are important processes that occur after vascular injury to contribute to endothelial dysfunction. Vascular injury occurs when the intima of a blood vessel is bruised by mechanical, chemical or biological agent resulting in appropriate response to restore homeostasis based on the kind of injury. Such injuries create avenues for interaction of cytokines with thrombotic, adhesive, haemostatic and inflammatory factors. In the case of injury due to infectious agents like the *Plasmodium* parasite, elevated levels of markers of endothelial activation have been reported (Hollestelle et al., 2006). Interestingly, the nature of endothelial activation and dysfunction observed for malaria has also been reported in diabetes mellitus (Vischer, 2006). Indeed, von Willebrand factor (VWF), an important activator of the haemostatic system (Margetic, 2012), also triggers inflammation and may link haemostasis to inflammation and serve as a biomarker for malaria (Hollestelle et al., 2006; Kim et al., 2011), insulin resistance (Kim et al., 2006) and diabetes (Vischer, 2006). Elevation of VWF due to endothelial activation and dysfunction, by malaria or diabetes results in the release of inflammatory markers (Hollestelle et al., 2006; Kim et al., 2011).

The link between malaria-induced inflammation and T2DM is not direct due to the complex nature of the inflammatory phenomenon in relation to the two conditions. However, several studies have reported positive associations of malaria-induced inflammation with critical risk factors of T2DM. For example, malaria-induced inflammation in placental malaria has been associated with low birth weight (LBW) (Fitri et al., 2015; Rogerson et al., 2007; Sharma and Shukla, 2017) and LBW is acknowledged as an important risk factor for development of T2DM in different populations (Johansson et al., 2008; Mi et al., 2017; Patti, 2013; Ruiz-Narváez et al., 2014; Xia et al., 2019). Also, malaria is positively linked to insulin resistance (Acquah et al., 2017b, 2014; Eltahir et al., 2010) mediated by inflammation (Acquah et al., 2016a; Moxon et al., 2013). Indeed, insulin resistance is a cardinal risk factor for the development of T2DM (Lontchi-Yimagou et al., 2013; Muoio and Newgard, 2008). Above all, inflammatory markers such as IFN-γ, TNF-α and CRP, which have been implicated in the development of insulin resistance (Abdel-Hamid et al., 2013; Aguirre et al., 2000; Gao et al., 2002; Peraldi et al., 1996) are involved in the pathogenesis of malaria (Acquah et al., 2016a; Mbengue et al., 2016; Nasr et al., 2014).

These observations which cannot be considered as coincidental findings, demonstrate indirect evidence and reinforce inflammation as a mechanism by which malaria may contribute to the development of T2DM. Indeed, the role of inflammation in the pathogenesis of T2DM through insulin resistance is well documented in several reviews (Khansari et al., 2009; Lontchi-Yimagou et al., 2013; Muoio and Newgard, 2008; Wellen and Hotamisligil, 2005) and primary papers (Acquah et al., 2016b; Lee et al., 2011). With the established possibility of chronic infection by the *Plasmodium* parasite (Hamainza et al., 2014) coupled with the acknowledged role of chronic inflammation in the development of obesity-related health conditions such as T2DM (Holland et al., 2011; Roe and Pasvol, 2009), the likely role of malaria in the development of T2DM condition through inflammation, can no longer be in doubt.

Oxidative Stress

Biochemically, life is perpetuated by a carefully regulated balance between synthetic and degradative processes to ensure normal cellular function. If the regulatory process is altered unduly, the expected balance is attenuated and normal cellular function is impaired. Oxidative stress occurs when there is an imbalance between reductive and oxidative processes in the cell. Reductive processes give rise to products that generally reduce the oxidation status of the cell and such processes result in the production of heterogeneous group of compounds generally referred to as antioxidants. Similarly, oxidative processes in humans result in increased concentration of oxidants generally called reactive oxygen or nitrogen species (ROS/RNS) and increased oxidative state of the cell. As such,

oxidative stress can be viewed as a situation where there is a disproportionate concentration of oxidants and antioxidants molecules in the cell. Indeed, oxidative stress, just like inflammation, is necessary for normal and effective cellular function. It becomes problematic only when it is dysregulated in a relatively prolonged manner. Oxidative stress can result from degradative or synthetic biochemical processes and is acknowledged to contribute to the development of several conditions of chronic (Owiredu et al., 2012; Roe and Pasvol, 2009; Stanek et al., 2010) and acute (Percário et al., 2012; Rawlingson et al., 2003) nature. In humans, oxidative stress is known to be caused by dysregulated balance between the activities of ROS/RNS and antioxidant systems. ROS are compounds of oxygen which may be radical or not but are reactive enough to cause cellular damage if unchecked. Such compounds of oxygen include hydroxyl radical ($^{\cdot}OH$), superoxide anion ($O_2^{\bullet -}$) and hydrogen peroxide (H_2O_2). Detailed information on formation, specific cellular organelles and enzyme systems that employ the ROS has been reviewed elsewhere (Halliwell, 2006; Moldovan and Moldovan, 2004). Similarly, nitric oxide ($NO^{\bullet}$), a compound of nitrogen, can chemically exist in three distinct forms as nitroxyl radical ($NO^{\cdot}$), nitrosonium (NO^{+}) and nitroxyl anion (NO^{-}) (Stamler et al., 1992) and reacts with a variety of cellular molecules to alter the redox environment of the cell in favour of oxidation. These separately reactive pro-oxidant chemical species of nitrogen constitute the RNS. Indeed, the role of RNS in the pathogenesis of diseases has been acknowledged (Moldovan and Moldovan, 2004; Voetsch et al., 2004).

Oxidative stress has been widely documented to be involved in the pathogenesis of diabetes and various obesity-associated health conditions (Hirata et al., 2011; Malik et al., 2013). Oxidative stress is not only involved in non-communicable diseases but in infectious diseases as well. For instance, infection by the *Plasmodium* parasite has been reported to cause decreased levels of antioxidant molecules (Acquah et al., 2016a; Erel et al., 2001; Griffiths et al., 2001) but increased levels of pro-oxidant molecules (Acquah et al., 2016a; Huber et al., 2002; Pabón et al., 2003). Although these reported cases reflect parasite-induced oxidative stress in the host as a pathogenic mechanism by the parasite, a similar imbalance can result from the host's defense mechanism aimed at getting rid of the invading parasite. Thus, oxidative stress can be helpful and harmful to both the host and the parasite and this delicate balance between pro-oxidants and antioxidants molecules is exploited in the management of several diseases.

The chemical species considered to be the most destructive among the ROS/RNS is the radical species. Radical refers to a chemical species with unpaired electrons in an atomic orbital which is capable of independent existence (Halliwell, 2006; Moldovan and Moldovan, 2004). Radicals are electron-deficient and attain stability by abstracting electrons from other chemical groups and transfer their radical status to them. Thus, when a radical species interact with a non-radical stable compound, the radical species takes an unpaired electron from the stable non-radical compound. As such, the radical becomes a chemically stable species due to the newly attained paired electron status resulting in the transfer of the radical status to the compound from which the unpaired electron was taken. This unpaired-electron abstraction and radical status transfer reaction can continue in a chain manner to disrupt effective cellular function if uncontrolled. The chain reaction is halted when the radical reacts with another radical to form a stable compound. Thus, radicals attain stability by losing the unpaired-electron status. The halting or quenching of radical-induced chain reaction or the prevention of its occurrence in the first place, is the major task of antioxidants.

Antioxidants area highly diverse group of compounds, that interact in a manner to reduce cellular oxidation status. They can be grouped into preventive antioxidants, scavenging antioxidants and enzyme antioxidants based on their mechanism of action (Tanja et al., 2008). Preventive antioxidants including albumin, caeruloplasmin, ferritin, metallothionine, myoglobin and transferrin, avert the formation of ROS/RNS. The scavenging antioxidants like ascorbic acid, α-tocopherol, β-carotene, bilirubin, glutathione and uric acid work to terminate the chain reaction induced by generated free radicals to eliminate the ROS/RNS. Above all, the enzyme antioxidants which include catalase, glutathione peroxidase, glutathione reductase and superoxide dismutase facilitate detoxification of the toxic non-radical components of ROS/RNS once they are formed. As such, the cell succumbs to the adverse effects of oxidative entities when one or more of these antioxidant components are compromised. Several evidence abound to demonstrate the critical role of oxidative stress in the pathogenesis of malaria (Percário et al., 2012; Rodrigues Henriques and Gamboa de Domínguez, 2012) or T2DM (Rains and Jain, 2011; Srivastava et al., 2005).

Indeed, the observation of reduced antioxidants enzymes (Becker et al., 2004; Sohail et al., 2007) and small molecules (Caulfield et al., 2004; Hassan et al., 2004; Metzger et al., 2001) in malaria coupled with elevated levels of peroxidation products (Acquah et al., 2016a; Cabrales et al., 2011), demonstrates the crucial role of oxidative stress in the pathogenic process of the *Plasmodium* parasite.

In obesity, a cardinal risk factor for the development of T2DM, similar findings of reduced levels of the various antioxidants systems have been reported in several studies (Bougoulia et al., 2006; Karaouzene et al., 2011; Mittal and Kant, 2009) to the extent that the presence of oxidative stress is reported to modify the structure and impair the function of insulin (Olivares-Corichi et al., 2011). These findings in obese subjects coupled with those in malaria, point to an expected exacerbation of oxidative stress in obese individuals who get malaria compared with their counterparts without malaria. Additionally, the findings point to a potential role for malaria in the development of T2DM through oxidative stress. As such, the interaction of malaria with obesity could escalate oxidative stress-induced insulin resistance and the eventual development of T2DM. Indeed, it has recently been demonstrated that insulin resistance

is establishment at a relatively reduced level of parasitaemia in a second episode of rat malaria due to a possible priming of infected cells after an earlier episode (Acquah et al., 2017a). Also, mammalian cells respond to diabetes or malaria-induced oxidative stress in a similar manner by doubling of total RNAs (Zhang et al., 2011). These reports further point to oxidative stress as a probable link between malaria and cardinal risk factors of T2DM.

Interestingly, the likely link between malaria and diabetes has even been recognized at the pharmacological level as biguanides continue to serve as the scaffold for the synthesis of various antimalarial and antidiabetic drugs, probably due to their metal-interactive and antiproteolytic properties (Sweeney et al., 2003) as well as their ability to inhibit oxidative phosphorylation (Bridges et al., 2014). Indeed, several antimalarial drugs exhibit hypoglycaemia as a side effect (Ogetii et al., 2010; Sweeney et al., 2003) and several antidiabetic drugs demonstrate antimalarial properties (Sweeney et al., 2003). Recently, Li et al. (2017) demonstrated that artemisinins, a potent group of antimalarials, inhibit secretion of glucagon by enhancing gamma aminobutyric acid signaling to transform α-cells to β-cells in the zebrafish, mouse, rat and human islet cells and these changes in the islets have been proposed to have the potential to reverse diabetic conditions (Purwana et al., 2014; Soltani et al., 2011). Putting together, malaria could be linked to diabetes at different levels that warrant further investigations.

Synergy between Inflammation and Oxidative Stress

The link between inflammation and oxidative stress has never been in doubt. Both processes are normal physiological developments employed by cells to ward-off invading pathogens or any attempt to distort cellular homeostasis. As such, their harmfulness in terms of disease development is only observed in dysregulated state. The presence of inflammation can lead to oxidative stress and vice versa. Indeed, inflammatory response to protect cells against invading pathogens involve oxidative stress, hence, the frequent reported occurrence of oxidative stress and inflammation under varied health conditions (Acquah et al., 2016a; Khansari et al., 2009; Roe and Pasvol, 2009). Likewise, excessive outburst of oxidative stress induces inflammation under varied cellular conditions (Copple et al., 2010; Pashkow, 2011; Roberts et al., 2010). Indeed, the development of T2DM through insulin resistance involves low-grade inflammation and oxidative stress of chronic nature (De Rooij et al., 2009; Khansari et al., 2009) probably mediated by leptin and adiponectin Acquah et al. (2017b); Sugiura et al. (2008); Zhou et al. (2011). In a longitudinal study involving 619 disabled women aged 65 years and above, interleukin-6 (IL-6), a potent pro-inflammatory cytokine exhibited both cross-sectional and longitudinal inverse associations with antioxidant carotenoids (Walston et al., 2005). At the molecular and cellular levels, tumor necrosis factor alpha (TNFα), an acknowledged pro-inflammatory cytokine, has long been reported to suppress the transcription and translation of catalase, a known anti-oxidant enzyme in rat (Beier et al., 1997). These observations clearly demonstrate that oxidative stress can indeed be facilitated by inflammatory process. This synergistic relationship between oxidative stress and inflammation is implicated in the pathogenesis of T2DM or malaria and their related complications (Du et al., 2013; Kowluru and Mishra, 2015) and even heightened in the coexistence of both conditions in the same individual (Acquah et al., 2016a). The synergy between oxidative stress and inflammation is postulated to link T2DM and malaria. For instance, several evidence suggest that placental malaria characterized by inflammation and oxidative stress is associated with negative pregnancy outcomes in both human and animal studies (Avery et al., 2012; Megnekou et al., 2015; Sarr et al., 2017; Umbers et al., 2011) and such outcomes, such as low-birth weight, increase the risk of developing obesity and T2DM in adulthood (Whincup et al., 2008). With inflammation and oxidative stress interacting synergistically in the pathogenesis of malaria and T2DM, it is not out of place for one to postulate that the predicted increased incidence of T2DM in the sub-Saharan Africa could be fueled at least, in part, by its malaria-endemic state.

Conclusion

Malaria perpetuates its pathological effects through inflammation and oxidative stress which contribute to the development of insulin resistance. The nature of malaria-induced oxidative stress and inflammation is similar to that observed in obesity, an important risk factor for the development of T2DM. Oxidative stress and inflammation function synergistically in malaria-induced insulin resistance. Various levels of evidence portray malaria as a potential diabetogenic risk factor that can interact with obesity to potentiate the development of T2DM. More research is needed to better understand the relationship between malaria and T2DM to ensure that efforts at controlling malaria impact positively on the fight against T2DM.

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