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ARTESUNATE AND ESOMEPRAZOLE ADD-ONS TO LOW-DOSE ASPIRIN IN THE PREVENTION AND TREATMENT OF PLACENTAL MALARIA, PRE-ECLAMPSIA, FETAL GROWTH RESTRICTION AND METABOLIC SYNDROME: A MECHANISTIC REVIEW AND CLINICAL REPORT

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ABSTRACT

Recent evidence indicates that malaria, type 2 diabetes mellitus and hypertension constitute a 'triumvirate' that significantly increases the suffering in Africa. The contribution of malaria to the alliance may be via the up-regulation of inflammatory and oxidative stress which attenuate factors of the insulin signalling pathway. Upregulation of immune-inflammatory cascade and Th_l/Th_{17} reponse is a common mechanism in severe malaria, placental malaria, pre-eclampsia, hypertension, type 2 diabetes mellitus, auto-immune diseases and fetal growth restriction with placental insufficiency. Safe drugs that attenuate inflammatory and oxidative stress, decrease Th_l/Th_{17} response, upregulate factors of the insulin signalling pathway and which kill the ring/early forms of the malaria parasite in the blood which particularly mediate the oxidative stress stand to be beneficial in these diseases. Rigorous supervision of malaria treatment with ACTs decreases umbilical artery resistance index in microscopic and submicroscopic placental malaria which has identical aetiopathogenic mechanisms with pre-eclampsia. The improved ACT campaign may have co-incided with the significant ($P< 0.05$) decrease in eclampsia rates observed 2012-2016. Artesunate, esomeprazole, low-dose aspirin, calcium and vitamin A supplementation may upregulate factors of the insulin signalling pathway, enhance the actions of heme oxygenase –I and endothelial nitric oxide. They thus deserve attention as emerging agents that additively may enhance insulin signalling, and down-regulate the immune-inflammatory cascade, angiogenic/anti-angiogenic imbalance in type 2 diabetes, hypertension, severe malaria, placental malaria, pre-eclampsia and fetal growth restriction.

KEYWORDS: Artesunate, Esomeprazole, Low-dose aspirin, Placental malaria, Pre-eclampsia, Fetal growth restriction, Metabolic syndrome.

INTRODUCTION

4O% of the world's population is at risk of malaria caused by *Plasmodium falciparum* with over 500 million cases annually associated with more than a million yearly fatalities.[1] Most transmission occurs in sub-saharan Africa where children and pregnant women are most negatively impacted. The multigenic and hypervariable *Plasmodium falciparum* erythrocyte membrane protein-I (pfEMP-I) family on the infected erythrocyte membrane is involved in cytoadherence to the chemokine CXCLI, thrombospondin, CI (complement receptor I), chondroitin sulphate-A (CSA), p-selectin, endothelial protein C receptor (EPCR), heparin sulphate, CD36 and ICAM-I.[2,3,4] Unlike other pfEMP-I, varCSA binds to CSA of placental endothelial cells.

The malarial parasite glycosylphosphatidylinositols (GPIs) inside the infected erythrocyte induce expression of the pyrogenic cytokines TNF-alpha, IL-I, and IL-6 in human macrophages. TNF-alpha as well as GPIs alone increase expression of E-selectin, ICAM-I and VCAM and the above-named adherence receptors which mediate binding via pfEMP-I.[5] Sequestration, auto-agglutination, resetting, cytokines-induced excitotoxicity, endothelial activation, materno-fetal barrier thickening, fibrinoid deposits contribute to vascular obstruction and hypoxia as found in severe malaria, cerebral malaria and placental malaria. Also, as in pre-eclampsia where there is

leukocyte activation; in severe malaria, GPIs, haemozoin, infected erythrocytes and especially ICAM-I mediate leukocyte-endothelial activation.[6,7,8] There is increased serum lactate and increased angiopoietin-2 (Ang-2) in severe malaria which increases endothelial activation and sensitizes endothelium to TNF-alpha-induced endothelial cell permeability.[9,10] Also, there is increased placental expression of Ang-2 and its receptor, tyrosine kinase receptor for immunoglobulin-like and EGF-like domain-2 (Tie-2) with lower Ang-I in pre-eclampsia and pre-eclampsia-intra-uterine growth restriction.[11] In addition, uric acid, which is a biomarker for pre-eclampsia, and produces a pro-coagulation state in *Plasmodium falciparum* malaria, is associated with endothelial activation and the decrease in thrombomodulin levels.[12]

Activated protein C is decreased in severe malaria and pre-eclampsia and contributes to the pro-coagulant state

Low thrombomodulin levels in brain and placenta in severe malaria is associated with less activated protein C (APC) with consequent more free thrombin for its other functions on activated endothelium. Increase TNF-alpha-induced thrombin formation enhances cytoplasmic activity of high-mobility group box-I(HMGB-I) (a master regulator of inflammatory cascades) and tissue factor (TF).[1] Malaria-associated loss of endothelial protein C receptor(EPCR) combined with parasite impairment of the EPCR-APC interaction promote coagulation, inflammation and endothelial barrier breakdown.[3,13] This endothelial barrier breakdown may be associated with high angiotensin (1-7) peptides which are reported to confer protection in cerebral malaria by increasing BBB integrity.[14] Thrombomodulin, activated protein C, protein Z, protein S levels are also low in women with pre-eclampsia and pregnancy complications,[15,16,17,18] and administration of thrombomodulin increases utero-placental perfusion in pre-eclampsia models. Activated protein C and insulin work in concert with VEGF and platelet-derived growth factor to activate PI3K/Akt and decrease diabetic complications.[19] There is an inhibitory role of the PI3K signalling pathway in VEGFR-2-induced tissue factor expression.[20]

Enhanced immune-inflammatory cascade in severe malaria, placental malaria and pre-eclampsia: An overlay of mechanisms

As in pre-eclampsia, placental malaria and IUGR are associated with excessive Th_I inflammatory responses, decreased membrane-bound HLA-G expression and aberrant activation of natural killer cells.[21,22,23,24,25] While natural killer cells (NK cells) stimulate recruitment of CXCR3+ T-cells to the brain during cerebral malaria,[26] decreased activation of uterine NK cells (uNK) by the low HLA-G is involved with elaboration of anti-angiogenic proteins in pre-eclampsia. There is increased pfGPIs-induced TNF-alpha via TLR-2, TLR-4, TLR-9, NF-kappa B and MAPK in placental malaria,[27] and increased TLR-9, TLR-7/8 and TNF in pre-eclampsia.[28,29,30] Furthermore, there is increased IFN-gamma- and TNF-alpha-induced CXCL10(IP-10) which is anti-angiogenic and chemotactic for Th_I lymphocytes in severe malaria and pre-eclampsia.[31,32,33,34] The interleukin-I receptor-like I soluble ST2 (sST2), a decoy receptor for IL-33 is associated with pre-eclampsia, experimental cerebral malaria and cardiac stress.[35,36]

TLR activation in pre-eclampsia and malaria may enhance C5a-induced pro-inflammatory response by negatively modulating the second C5a receptor, C5L2.[37,38] C5a-induced signalling via HMGB-I is a potent inducer of anti-angiogenic sENG, sFlt-I and increased Ang-2/Ang-I ratio in human malaria and placental malaria.[39,40,41,42,43,44,45] GM-CSF leads to TNF-alpha increases in cerebral malaria and its induction by TNF-alpha in pre-eclampsia plays a role in macrophage and dendritic cell activation which links innate immunity to acquired immunity.[46,47] Thus similarity in angiogenic profiles between pregnancy-associated malaria and pre-eclampsia has been reported to be associated with the reduced placental perfusion and low PAPP-A in the two illnesses.[48] The increased complement activation in the two illnesses is associated with increased anti-angiogenic profiles and oxidative stress which induces trophoblastic cell death and excitotoxicity.[49] It has been noted that immune activation, especially in the second infection in children and primary infection in non-immuned adults, may be more important in malarial pathology where the excessive IFN-gamma-induced increase in TNF-alpha now fails to control the parasitaemia but activates an immunopathology.[50,51] In concert, increaed haemozoin, free heme, ferritin and arginase serve to amplify the immunopathology.

Oxidative stress in malaria and pre-eclampsia impair insulin signalling

There is increased oxidative and endoplasmic reticulum stress due to the inflammatory process, free iron, free heme, free DNA, which upregulate ROS, RNS and ischaemia-reperfusion in pre-eclampsia, severe malaria and fetal growth restriction.[52,53] These serve to attenuate mitochondrial function and insulin signalling pathway (Figure.I).[54,55,56,57,58,59] Haemolysis in malaria increases arginase levels which decrease endothelial nitric oxide levels.[10] Enhanced TLR-9 provokes inflammation in response to fetal DNA and this may be the mechanism for fetal loss in preterm birth and pre-eclampsia.[60] The phosphatidylinositol-3 kinase signalling (PI3K-Akt) pathways exerts protective effects in malaria and loss of Akt activity increases sEng release in pre-eclampsia associated with low Tregs.[61] Although, Tregs may not be decreased in malaria, they are rapidly overwhelmed in severe infections.[62] In fact, sex-related low Tregs have been observed in malaria that is associated with higher IFN-gamma responses.[63]

There is evidence of insulin resistance in uncomplicated malaria with increased oxidative stress markers such as C-reactive protein.[64,65] Malaria is associated with high blood pressure via increased expression of inflammatory and oxidative stress markers and a malaria-high blood pressure hypothesis has been formulated which may be partly due to the high levels of angiotensin-II in severe malaria.[14,66,67]

Figure I: Low-dose artesunate, esomeprazole and low-dose aspirinupregulate eNOS signalling to PPARs to enhance heme oxygenase -I, mitochondrial biogenesis, lipid oxidation anti-malarial activity

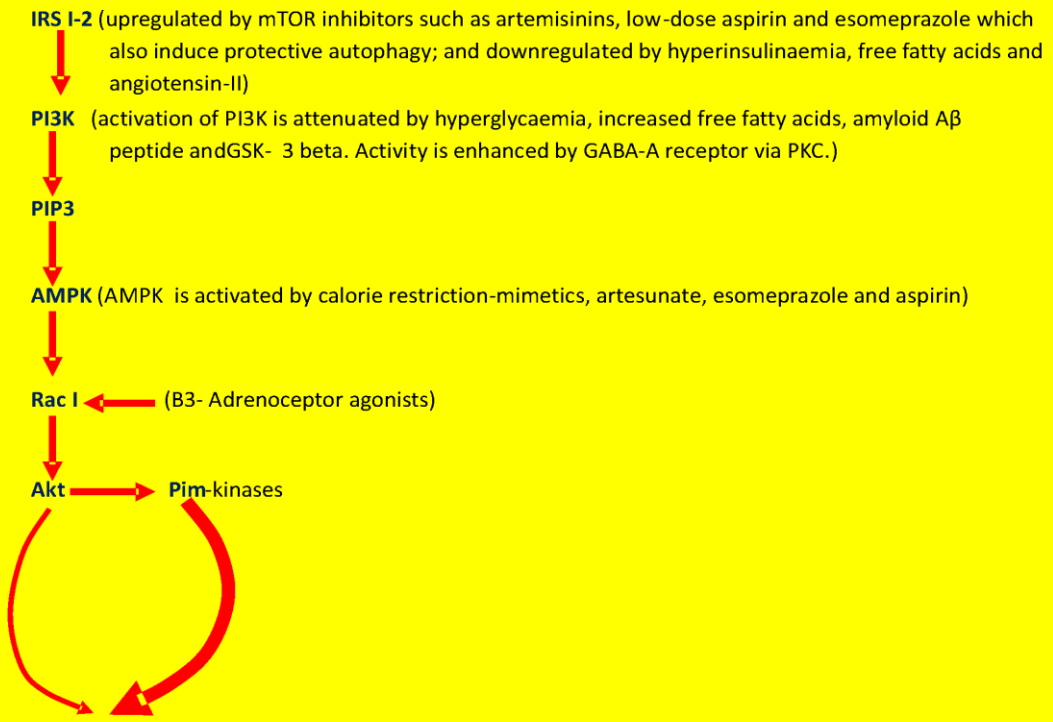

Figure I: *The SIMPLIFIED INSULIN SIGN ALING PATHWAY* : Metformin, mTORCI inhibitors, esomeprazole, low -dose artesunate, hydrogen sulphide, pravastatin, thiazolidinediones, calcium, exercise, calorie restriction -mimetics, GABA-A receptor agonists and low-dose aspirin activate PPAR alpha signal ling via AMPK activation. Insulin receptor substrate (IRS1/2 -PI3K-AMPK-eNOS-SIRTI-PGC-I alpha -EER-alpha-PPAR-Rs (^{o}/δ/β/α)-Vitamin D receptor signaling is important for mitochondrial function and lipid oxidation.This signaling pathway is enhanced by NF -kappa B inhibitors such as calorie restriction, exercise training, low -dose artesunate, low-dose aspirin and esomep razole. The signalling pathwayincreases levels of heme oxygenase -I and endothelial nitric oxide, thereby attenuating the effects of TLR -4/ROS/mTOR/MMPs/GSK-3- beta signaling which poses risk for hypertension, atherosclerosis, coronary artery disease, strok e and seizure susceptibility. Angiotensin attenuates heme oxygenas -I mRNA in a calcium -dependent manner. Malaria parasitaemia induces attenuation of the insulin signalling pathway,and enhances oxidative stress via ROS and RNS. Normal insulin signalling pathway downregulates malaria parasitaemia -induced increased oxidative stress and increased angiotensin-II levels..

The insulin signalling pathway is attenuated in malaria-, pre-eclampsia-induced oxidative stress and metabolic syndrome with attendant decreased heme oxygenase-I and endothelial nitric oxide

Therapeuticall targeting mitochondrial redox signalling may alleviate reactive oxygen species- and reactive nitrosative species-induced endothelial dysfunction in pre-eclampsia, which has similar aetiopathogenesis with the metabolic syndrome,[68] placental malaria and fetal growth restriction,[59] which are also associated with late-life development of the metabolic syndrome.[69]

i) Host AMPK is deleterious to intra-cellular growth and replication of Plasmodia spp.[70] AMPK activators and mTOR inhibitors such as calorie restriction-mimetics, methylene blue, sulforaphane, retinoic acid, rapamycin, metformin, artemisinins, salicylates and rosiglitazone inhibit parasite growth and reduce malarial parasitaemia.[71,72,73,74,75] Mammalian target of rapamycin (mTOR) inhibitors attenuate cerebral malaria and the new mTOR inhibitors, torins, are potent anti-malarials against the liver and blood stages.[76,77] Sporozoites infection of hepatocytes activate mTOR.[76]

ii) PI3-K/Akt activation exerts protective effects during sepsis by controlling C5a-mediated activation of the innate immune system.[78] Atorvastatin enhances PI3-K/Akt and eNOS to prevent *Plasmodium falciparum* cytoadherence and endothelial damage.[79] Artemisinins activate GABA-A receptor which enhances pancreatic β-cell neogenesis via inhibition of the master regulator of transcriptional activity *Arx*;[80] and enhances PI3K/SirtI signalling via protein kinase C.[81] GABA-A attenuates Th_1 responses and increase Tregs which may be low in malaria and pre-eclampsia. GABA-Aergic signalling also inhibits cytotoxic CD4+ T-cells and CD8+ T-cells and this is beneficial in severe malaria. Both endogenous and inducible nitric oxide inhibit cysteine protease of plasmodia and HO-I helps maintain bioactive levels of endogenous nitric oxide.[82]

iii) Autophagy induction by metformin, esomeprazole, low-dose artesunate, calcium, Vitamin D_3 and low-dose aspirin degrade kelchin-like ECH-associated protein-I(keap-I) which sequesters Nrf-2 in the cytoplasm, thereby allowing nuclear accumulation of Nrf-2.

iv) PPAR-gamma-retinoid X receptor agonists increase CD36-dependent phagocytosis of *Plasmodium falciparum* in parasitized erythrocytes and decrease malaria-induced TNF-alpha secretions by monocytes and macrophages.[51]

Multiple pathways regulate heme oxygenase -I(HO- I) activity

HO-I possesses anti-malarial,[83,84] anti-oxidant,[85,86] anti-hypertensive,[87,88] anti-autoimmune,[89] and angiogenic activities and its regulation is via multiple pathways.[90,91]

a) AMPK activation phosphorylatesnuclear factor-erythroid 2 p45-related factor 2(Nrf-2) at the Ser 550 residue and this coupled with AMPK-mediated GSK-3 beta inhibition promotes nuclear import (accumulation) of Nrf-2 to attenuate endoplasmic reticulum stress, [92]and for anti-oxidant response element (ARE)-driven gene transactivation;[93] which in part contributes to HO-I release.[94] AMPK and FoxO also inhibit NF-kappaB to induce nulear import of Nrf-2.[95] By inhibiting NF-kappa B and activating AMPK, the PPI esomeprazole may increase nuclear accumulation of Nrf-2, decrease inflammatory cytokines, increase HO-I levels, insulin release/sensitivity and enhance mitochondrial function (see Figure I). Low-dose aspirin and low-dose artesunate also exhibit these functions.

b) HO-I release is also mediated through by an upstream PI3K/Akt signalling pathway,[96] and by anti-oxidants-induced Nrf-2 phosphorylation at Ser 10in response to PKC but this may not lead to its nuclear import.[97]

c) Class III protein deacetylase Sirt I is induced by calorie restriction and upregulates Nrf-2 by attenuating the actions of (kelchin-like ECH-associated protein-I(Keap-I).[95]

d) Activation of Akt, HSP 90 (induced by anti-oxidants) and endothelial nitric oxide promote nuclear import of Nrf-2 via their modification of Keap-I.[98,99] Statins,[100] thiazolidinediones,[101] artesunate,[86,102,103] aspirin,[104,105] PPIs such as pantoprazole, esomeprazole and lansoprazole,[106][107][108] hydrogen sulphide,[109] calcium,[110] cis-9-retinoic acid,[111] vitamin D,[112] exercise,[113] nitric oxide, carbon monoxide and hydrogen sulphide enhance nuclear import of Nrf-2 for anti-oxidant defense.[114] The anti-oxidant nitric oxide is beneficial in severe malaria and pre-eclampsia.[115] Some of these agents are more specific and safer than others in enhancing nuclear accumulation of Nrf-2. For example, esomeprazole may be more specific than artesunate. Endogenous priming of the anti-oxidant system by moderate exercise may confer more health benefits than exogenous supplement of anti-oxidants.[113]

e) Estrogen receptor signalling and the PI3K/Akt pathway are involved in eNOS activation which rapidly upregulates Nrf-2.[116]

f) Calcium enhances the levels of Nrf-2 via its transactivation by specifically enhancing nuclear import of Nrf-2/ras GTPase activating-like protein-I (IQGAP-I).[117] It also has the same action as the vitamin A metabolite, cis-9-retinoic acid which synergistically with PPAR-gamma enhance tertiary butylhydroquinone (tBHQ)-mediated increase in Nrf-2.[118]

g) L-arginine, erythropoietin, nitric oxide, statins which upregulayte nitric oxide and levamisole which inhibits CD36 to decrease cytoadherence.[119]

h) Antagonists of IL-17 such as AMPK and PPAR-gamma inhibit ROS-induced upregulation of TH_{17}-producing IL-17,[120] attenuate IL-6 and enhance Nrf-2/HO-I to induce mitochondrial biogenesis.

Artesunate, esomeprazole and low-dose aspirin are safe in pregnancy, attenuate malaria parasite growth and enhance HO-I levels

The above illustrates that artesunate and esomeprazole as add-ons to aspirin and/or calcium may be beneficial in halting the growth of *Plasmodium falciparum* and preventing pre-eclampsia and this may involve several mechanisms. They may synergistically enhance optimal HO-I levels which is beneficial in hypertension, diabetic complications, malaria, placental malaria, pre-eclampsia and IUGR. The combination of PPIs with artesunate may decrease incidence of resistance which is the problem associated with use of artesunate for any other condition apart from malaria.[121] PPIs are reported to inhibit multi-drug resistance protein associated with drug resistance to pyrimethamine and chloroquine in malaria infection.[122] mTOR inhibitors and AMPK pathway activators that induce autophagy and upregulate HO-I such as calorie restriction, esomeprazole, low-dose artesunate and low-dose aspirin enhance resistance to malaria.[71,123] Aspirin by down-regulating parasite burden, inflammatory mediators and coagulation confer resistance in malaria.[124] Previously, a polypill concept has been put forward in the prevention of hypertensive disorders in pregnancy.[125]

Artesunate is more beneficial than quinine as first line agent against malaria

Workers have demonstrated that artesunate clears malarial parasites in blood faster than quinine.[126] Artesunate shows more efficacy than quinine in the critical early phase (first 24 hours) of malaria infection, arresting the ability of young parasites to mature to more damaging forms. Artesunate prevents cytoadherence and kills the non-adhesive ring forms, mainly responsible for inflammatory-oxidant stress in circulation, faster than quinine which only kill the adult parasites in parasitized red blood cells.[119] Intermittent preventive treatment in Senegal with sulfadoxine-pyrimethamine-artesunate (IPTc) and Ghana (IPTp) has resulted in decline of malaria, placental malaria; and IPTc may further prevent increased resistance.[127,128] SNP polymorphisms of the $pfdhf_s$ and $pfdh_f$ genes may confer resistance to sulfadoxine and pyrimethamine respectively.[128] Artemisinins upregulate endothelial nitric oxide and upstream kinases including Akt, AMPK and PGC-I alpha and enhances nuclear import of Nrf-2 to increase HO-I.[129] These considerations make artesunate, which is reported safe in first trimester,[130,131,132] unique in prevention of adverse pregnancy outcomes and in the prevention and management of placental malaria, pre-eclampsia and IUGR in Africa. Rigorous treatment of microscopic and submicroscopic malaria by ACTs decreases umbilical resistance associated with placental malaria and the low cerebroplacental Doppler ratio associated with small-for-gestational-age babies and low-birth weights.[133] Moreover, artesunate, via effects in man and in the mosquito, reduces post-treatment transmission of *P.falciparum*.[134,135] Esomeprazole is a drug used in treatment of peptic ulcer disease (PUD) and no significant adverse effect has been reported when used in pregnancy.[136] It has a beneficial role in pre-eclampsia.[136,137,138] Additionally, esomeprazole exhibits anti-malarial effects inhibiting the ATP synthase of the parasite.[139] A synergistic *in vitro* anti-malarial activity of the PPI omeprazole and artemisinins has been reported.[121] Low-dose aspirin started after 12 weeks is reported recently to be associated with decreased rate (30% decrease) of pre-eclampsia.[140,141,142]

There is a changing profile of eclampsia as the leading cause of maternal mortality rate in Australia and our locality with pulmonary embolism as the present leading cause in Australia and obstetric haemorrhage as the leading cause in Nigeria.[143,144] This may be due to the advanced obstetric care and sophisticated detection of risk factors and their prevention in Australia; while the observed decrease of eclampsia rate as a leading cause of adverse pregnancy outcomes/MMR rate in Nigeria has co-incided with better awareness of the ACTs in treatment and prophylaxis of malaria.[132,145] The Abuja Declaration of the Africa Summit on Roll Back Malaria (RBM), held April 25, 2000 in Abuja, Nigeria helped formulate the *National Anti-malarial Treatment Policy* which had as its principal objectives to halve the malaria mortality by 2010, at least 60% good access by 2005 to anti-malarial treatment and prevention of resistance to anti-malarial drugs. Our retrospective study in five satellite centres indicates decreased rates of eclampsia since the introduction and better awareness of artemisinin-based combination therapy; which may be supplemented with low-dose aspirin and/or calcium (Table I). Drugs that enhance mitochondrial biogenesis attenuate mitochondrial dysfunction associated with pre-eclampsia/IUGR spectrum, type 2 diabetes mellitus and acquired epilepsy.[146,147] Our laboratory-based studies have demonstrated the efficacy of artesunate in decreasing uric acid and glucose levels of streptozotocin-associated type 2 diabetes mice models and inhibiting epileptogenesis in mice models of epileptogenesis.[148] Additionally, artesunate, not metformin,[149] additively enhanced the effects of ceftriaxone to upregulate the anti-excitotoxic index of GABA-A/glutamate to attenuate epileptogenesis in our mice models. Artesunate-induced decrease of uric acid levels lead to NF-kappa B inhibition and upregulation of the anti-oxidant Nrf-2.[150] Low-dose artesunate administered chronically stand to give benefits in eclampsia prevention since it enhances GABA-Aergic neurotransmission. The addition of esomeprazole to the combination of artesunate and aspirin may help reduce incidence of resistance to artesunate and stands to significantly reduce severe malaria, pre-eclampsia, placental malaria in women and IUGR rates.[121,122,139]

Pre-eclampsia may increase type 2 diabetes mellitus and hypertension rates

There may be a bi-directional relationship between type 2 diabetes mellitus-hypertension (metabolic syndrome) and pre-eclampsia in women. They display overlapping

aetiopathogenic mechanisms,[147,151,152,153] where endoplasmic reticulum stress and inflammatory – oxidative pathways are crucial factors.[59,154] Cardiovascular risk factors, which may persist, are upregulated in women and offspring after pregnancies complicated by pre eclampsia or diabetes mellitus.[155] Aberrant NF-kappa B activation in gestational diabetes and hypertension by angiotensin-II ATI receptors represses the IL-6 and TLR-4 inhibitor microRNA-98/*lethal-7* (Let-7) with consequent increased induction ofNF-kappa B production of IL-6 to initiate type 2 diabetes and hypertension respectively and a variably orchestrated inflammatory chaos.[152,156,157] Also and significantly, there is angiotensin-II upregulation in hypertension, type 2 diabetes, intra-uterine growth restriction and malaria which increase NF-kappa B levels with consequent attenuation of heme oxygenase-I levels and pancreatic insulin secretion. In pre-eclampsia, the presence of angiotensin-I agonistic antibody (ATI-AA) which induce SFlt-I coupled withthe increase in angiotensin-II sensitivity and decrease in angiotensin (1-7) peptides has a negative impact on heme oxygenas-I level important for cardiovascular integrity.[14,147] Angiotensibn II may be protective (via angiotensin (1-7) peptides) against malaria- increased oxidative stress and BBB leakage, but may be pro-hypertension and pro-excitotoxicity via the ATI subtype receptors,[158,159,160,161,162] which may be the cause of the decreased responsiveness of the renin-angiotensin system in blacks to angiotensin converting enzyme inhibitors.[163] High salt intake amongst blacks, through sodium-mediated increased sensitivity to angiotensin-II, of course, has a compounding effect. Malaria-parasitemia and angiotensin II-induced- IL-17 production also cause NF-kappa B activation, including activation of TNF-alpha and IFN-gamma and decreased IL-10 and TGF-beta. The reinforcing roles between angiotensin-II and IL-17 may be the regulating link between auto-immune diseases, obesity-hypertension, gestational diabetes mellitus, type 2 diabetes mellitus, pre-eclampsia, placental malaria and intra-uterine growth restriction.[164,165,166,167,168,169,170] Angiotensin receptor blockers (ARBs) such as losartan (a specific blocker of angiotensin ATI receptor) inhibits Th_1 and Th_{17} polarisation *and induces potent regulatory T-regs*. Th_1 and Th_{17} helper cells which produce IL-17 have overlapping and collaborative roles.[171] Through AMPK activation, artesunate, aspirin and esomeprazole may also attenuate angiotensin II ATI receptor subtype signalling via PKC, positively influence Th_{17}/T-reg balance and block IL-17/IL-6 positive feed-back.[172]

Apart from attenuating malaria, hypertension and type 2 diabetes, AMPK activation and enhanced insulin signalling pathway by artesunate-esomeprazole add-ons to aspirin may decrease insulin-like growth factor-I (IGF-I), IL-17 levels and increase IGF-IBPs, Tregs which are dyregulated in diseases associated with the metabolic syndrome (obesity and disorders of adipose tissue) such as obesity-hypertension, type 2 diabetes, acute coronary syndrome, colo-rectal carcinoma (CRC) and osteoarthritis. Thus, artesunate and artesunate add-ons to low-dose aspirin may prevent not only type 2 diabetes, auto-immune diseases, cancers and major cardiovascular events but also malaria, placental malaria, pre-eclampsia/eclampsia and fetal growth restriction.[172,173,174,175]

Table I: Number of eclampsia referrals from 5 satellite centers, 2012-2016.

	2012	2013	2014	2015	2016
Number of eclampsia patients referred	5.53 ±3.10	4.46 ±2.20	2.00 ±1.90	1.60 ±2.60	1.80 ±2.10

Table 1: Nnumber of eclampsia referrals showed showed a significant ($P < 0.05$: Unpaired t-test) downwards trend (2012-2016). The Roll-Back-Malaria campaign started in 2000, with one of its aims being to create at least 60% awareness to ACTs by the year 2005.

Malaria-induced oxidative stress may enhance overactivation of poly-(ADP ribose) polymerase to cause mitochondrial dysfunction, decrease in insulin signalling and genomic instability

Malaria-induced oxidative stress increases inducible nitric oxide (iNOS) which through peroxynitrite enhances nuclear-to-cytoplasmic movement of HMGB-I, cause overactivation of poly-(ADP ribose) polymerase to cause genomic instability, DNA damage, decreased mitochondrial function and decreased insulin signalling.[176] Artesunate attenuates mitochondrial-to-nuclear stress induction through activation of $ERK_{1/2}$ - CREB signalling, decreases mitochondrial DNA damage and restores abnormal changes in nuclear morphology by inhibiting β-amylod-induced apoptosis. [177,178] Similar to metformin, esomeprazole, low-dose aspirin, low-dose artesunate-mediated down-regulation of poly-(ADP ribose) polymerase may induce the inhibition of NF-kappa B and enhanced SIRT-I levels. This serves to positively impact retrograde mitochondrial-to-nucleus stree signalling as well as anterograde nucleus-to-mitochondrial signaling,[179,180] both needed for cellular homeostasis and insulin sensitivity.[181,182,183]

CONCLUSION

Present evidence shows that low-dose artesunate and esomeprazole and low-dose aspirin combination therapy enhance the anti-oxidant role of the Nrf-2-ARE-HO-I axis which also upregulates the insulin signalling pathway to enhance mitochondrial biogenesis; and attenuate malarial pathogenesis which is important in inducing oxidant stress.

Community-based trials of artesunate, esomeprazole as add-ons to low-dose aspirin may yet prove their role as a worthwhile combination therapy that may protect against

and reduce the burden of placental malaria, pre-eclampsia, HELLP, APS, IUGR, type 2 diabetes mellitus and hypertension in women of child-bearing age.

The well-deserved further appraisal of the combination therapy in the prevention/treatment of malaria - metabolic syndrome spectacle and aftermaths in the population at large is critically compelling.

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