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# Changes in Serum Glucose and Triacylglycerol Levels Induced by the Co-administration of Two Different Types of Antimalarial Drugs among Some *Plasmodium falciparum* Malarial Patients in Edo-delta Region of Nigeria

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## ABSTRACT

The aim of study was to show the changes in serum glucose and TAG levels in patients receiving anti-malarial treatment as well as changes caused by therapeutic drug type. One hundred individuals were investigated comprising of 40 apparently healthy control individuals, 40 malarial infected patients receiving either one or two types of anti malarial treatment and 20 *P. falciparum* infected patients but yet to be treated, using standard procedures for Glucose and Triaclyglycerol estimation. Results showed significantly reduced ($p<0.05$) serum glucose (4.02±0.80 mmol $L^{-1}$) and TAG (1.27±0.54 mmol $L^{-1}$) in malarial infection when compared with the control values (5.22±0.67 mmol $L^{-1}$ and 1.50±0.56 mmol $L^{-1}$) from apparently healthy subjects and intake of anti-malarial drugs raised serum glucose (4.80±0.60 mmol $L^{-1}$) when compared with values for those infected but yet to be treated (4.02±0.80 mmol $L^{-1}$), although this value was still lower than that for the healthy control subjects. However anti-malarial treatment increased serum TAG (1.67±0.81 mmol $L^{-1}$) even above the level observed for the healthy subjects (1.50±0.56 mmol $L^{-1}$). Glucose (4.72±0. 52 mmol $L^{-1}$) and TAG (1. 97±0.92 mmol $L^{-1}$) levels were higher in patients receiving two different types of anti-malarial drugs (artesunate/coartem, lonart/camoquin, artesunate/fansider) compared with those receiving only one type of anti-malarial drug (artesunate, coartem, camoquin, lonart). The results suggest that malarial infection significantly ($p<0.05$) reduces blood glucose and TAG levels but treatment with especially two different types of anti-malarial drug raised blood glucose and TAG levels. Combination of two different types of anti-malarial drug in the treatment of malarial infection could significantly improve the hypoglycemic risk but it's highly exaggerated influence on serum TAG may be worrisome.

**Key words:** Glucose, *P. falciparum*, triacylglycerol (TAG), treatment, anti-malarial

## INTRODUCTION

Malarial is a vector-borne infectious disease caused by protozoan parasite which has overtime been a point of concern and in recent times received a lot of attention due to it's widespread nature in tropical and subtropical regions, including parts of America, Asia and Africa. Each year, there are approximately 515 million cases of malarial, killing between one and three million people, the majority of whom are young children in sub-Saharan Africa (Snow *et al*., 2005).

The disease is caused by protozoan parasite of genus *Plasmodium* with the most infectious form caused by *P. falciparum*. The primary host of the parasite is the female *Anopheles* mosquito and has infected people for over 50,000 years (Joy *et al.*, 2003). Close relative of the human malarial parasite remain common in chimpanzees (Escalante *et al.*, 1998). Malaria is presently endemic in a broad band around the equator; however, it is in sub-Saharan Africa where 85-90% of malaria fatalities occur. Malaria is common in rural areas and pregnant women are most especially vulnerable. Despite efforts to reduce transmission and increase treatment, there have been little changes in infection rate in areas at risk of this disease since 1992 (Hay *et al.*, 2004). Indeed, if the prevalence of malaria stays on its present upward course, the death rate could double in the next twenty years (Breman, 2001). No vaccine is currently available for malaria and preventive drugs must be taken continuously to reduce the risk of infection (Hull, 2006).

Treatment of malaria involves supportive measures as well as specific anti-malarial drugs. Chemotherapy is the primary means of treating protozoan infections. Successful chemotherapy depends largely on the ability to exploit metabolic differences between the pathogens and the host. A number of drugs used as prophylaxis against or treatment for malaria have chemical significant metabolic side-effects. Of these, hypoglycemia resulting from quinine administration is one of the most important (Warrel *et al.*, 1990). Quinidine the diastereoisomer of quinine can also cause this complication. The 4-aninoquinoline chloroquine is known to influence glucose metabolism in ways which could lower blood glucose concentration (Smith *et al.*, 1987).

Recently quinoline methanol, mefloquine has been shown to reduce plasma glucose concentration during conventional prophylactic course in healthy young adults (Davis *et al.*, 1996). In all these situations, raised serum or plasma insulin concentration has been observed on which maintenance of appropriate blood glucose level is dependent. Observation has also shown that blood lipid of level which triacylglycerol (TAG) is a basic constituent is related to the amount of serum insulin, though little attention has been paid to the effect of anti-malarial drugs on serum lipid. This study seeks to show the changes in serum glucose and TAG levels in patients receiving anti-malarial treatment as well as changes caused by therapeutic drug type whether one or two different anti-malarial drug treatment.

## MATERIALS AND METHODS

**Subjects:** A total of 100 subjects (50 males and 50 females) were used for this study. Forty of the subjects were *P. falciparum* malarial infected patients receiving either one type or two different types of anti-malarial drugs of either artesunate, coartem, carmoquine or lonart. Forty apparently healthy individuals and 20 other individuals infected with *P. falciparum* but yet to be treated were included as control groups. Informed verbal consent was sought and obtained from the volunteers (or guardians) whose ages range from 5-60 years who were from Faith medical center Benin and University Health center Delta State University Abraka Delta state. The study was between March 2009 and September 2009.

**Sample collection:** Three specimen bottles were used to collect blood specimen from each subject. Fluoride oxalate bottles for blood glucose determination, plain sterile bottles for serum triacylglycerol (TAG) estimation, EDTA (ethylene diamine tetra acetic acid) bottles for malaria parasite count. Blood samples were collected by clean venepuncture technique from the antecubital fossa into already labelled bottles with undue pressure on either the arm or the plunger of the

syringe. Samples in the fluoride oxalate bottles were tested immediately for glucose while samples in the plain tube were allowed to clot and then centrifuged at 1200 xg for 5 min at room temperature (28-31°C) to obtain sera samples for triacylglycerol determination. Samples in EDTA anticoagulant bottles were tested immediately for malarial parasite after staining the thick film with Giemsa stain.

Specimen Analysis: The malaria parasite count was done by examining a thick blood film stained with Giemsa stain (Cheesbrough, 1998). Blood glucose estimation was carried out using the glucose oxidase method (Berham and Trinder, 1972). Triacylglycerol estimation was done by the enzymatic method (Carstensen, 1985) using the reflotron analyzer.

**Statistics:** Data were analyzed using analysis of variance (ANOVA) and correlation performed by SPSS version 16 statistical software. Results were expressed as Mean±Standard Deviation (±SD).

## RESULTS

Malaria infection significantly reduced ($p<0.05$) serum glucose and TAG when compared with the control values obtained from the apparently healthy subjects. Intake of anti-malarial drugs increased serum glucose when compared with the values for those infected but yet to be treated, but still lower than the healthy control level. Serum TAG for malarial infected patients receiving treatment was highest when compared with those infected without treatment and the healthy subjects.

Serum glucose and TAG levels were higher for the female subjects irrespective of the groups but malaria infected male patients receiving anti-malaria treatment had higher amount of serum TAG. There are no significant age-related changes in serum glucose and TAG but overall, effect of malarial infection on the reduction in serum glucose and TAG was most severe among those between 0-15 years:

- **Artesunate:** It is active component is artemesinin (dehyroartemesinin). Reduces parasite gematocytes transmission and Inhibits protein synthesis via DNA replication in the parasite
- **Coartem:** It is active components include artemether and halofantrine- forms cytotoxic complexes with faritoporphyrin IX that causes plasmodia membrane damage
- **Lonart:** It contains arthemether and halofantrine. Has same action as coartem
- **Fansider: Sulfadoxine (500 mg) and pyrimethamine (20 mg):** It inhibits dehydrofolate reductase in the parasite thus preventing the biosynthesis of purines and pyrimidines, halting DNA synthesis, cell division and reproduction of parasite
- **Camoquine: Amodiaquine HCl (200 mg) (4 aminoquinolin):** It controls the conversion of toxic heam to hemozion by inhibiting the biocrystallization of hemozoin thus poisoning the parasite through excess levels of to toxicity and interfere with parasite nucleic acids

Glucose and TAG levels were higher in patients receiving two different types of anti-malarial drugs compared with those receiving only one types of anti-malaria drugs. These values were still lower than those for the non-infected healthy subjects but higher than the levels found among the infected subjects, yet to be treated.

The TAG value for those receiving one type or two different types of anti-malarial drugs was higher compared with either the healthy control values or the value for the malarial infected patients who are yet to be treated (Table 1).

Table 1: Changes in Glucose and TAG levels among *P. falciparum* infected patients receiving one or two different types of antimalarial drugs

| | Bioanalytes | | | |
|---|---|---|---|---|
| | Glucose (mmol $L^{-1}$) | | TAG (mmol $L^{-1}$) | |
| Anti-malarial drug type | Male | Female | Male | Female |
| **One type (n = 25)** | | | | |
| Artesunate | 4.15±0.61 | 4.20±1.37 | 1.06±0.15 | 0.92±0.13 |
| Coartem | 4.00±0.52 | 4.04±0.40 | 1.39±0.25 | 1.20±0.04 |
| Camoquine | 3.81±0.10 | 4.01±0.42 | 1.50±1.38 | 1.02±0.16 |
| Lonart | 4.13±0.04 | 4.26±0.16 | 2.01±0.31 | 1.82±0.08 |
| Average | 4.02±0.32 | 4.13±0.60 | 1.49±0.52 | 1.24±0.10 |
| **Two types (n = 15)** | | | | |
| Artesunate/Coartem | 4.57±0.68 | 4.80±1.04 | 2.25±1.62 | 1.50±1.04 |
| Artesunate/Fansider | 4.16±0.11 | 5.09±0.42 | 2.62±0.13 | 1.55±1.30 |
| Lonart/Camoquine | 4.25±0.64 | 5.42±0.20 | 2.16±1.3 | 1.73±0.10 |
| Average: | 4.33±0.48 | 5.10±0.55 | 2.34±1.02 | 1.60±0.81 |
| Malarial infected subjects yet to be treated | 3.93±0.51 | 4.26±0.46 | 1.12±0.35 | 1.43±0.73 |
| Healthy subjects | 4.91±0.61 | 5.54±0.74 | 1.41±0.61 | 1.62±0.51 |

Results are expressed as a Mean±SD

## DISCUSSION

The results of this study show reduction in serum glucose levels in patients receiving anti-malarial treatment ($p>0.05$) and in malarial infected patients yet to be treated ($p<0.05$), when compared with the level obtained from the healthy control subjects (Table 2). Malarial infected patients (children between 0-15 years) had the highest considerable risk of hypoglycemia. The co-administration of two different types of anti-malarial drugs appears to significantly reduce the risk of hypoglycemia when compared with the administration of one type of anti-malaria drug (Table 1). Reduction in blood glucose level and subsequently, hypoglycemia is a well recognized complications of *Plasmodium falciparum* malaria and it's treatment (White *et al*., 1983). This has been observed to be particularly common among children, pregnant women and patients with severe malaria and hyper parasitaemia.

*Plasmodium falciparum* induced reduction in blood glucose could be due to the invasion of the liver cells by the malarialparasite which can cause organ congestion, sinusoidal blockage and inflammation of pancreatic cells (Jarike *et al*., 2002), leading to increased intracellular insulin, accumulation and slow receptor recycling (Herbert, 2002).

Malarial infected patients receiving anti-malarial drug had increased serum TAG but the level for those yet to be treated was lower when compared with the value for the non-infected (control) subjects (Table 2). These findings are consistent with earlier reports (Miller *et al*., 2002), although there are claims of higher level of lipids in malaria infected patients (Maegraith, 1981) based on the fact that *Plasmodium* genome contains gene encoding enzymes of phosphohpids metabolism allowing *de novo* synthesis of phosphatidylcholine via the kneddy pathway necessitating only uptake of a small amount of choline molecule from the host (Maegraith, 1981). However, explanation for the observed lower concentration of TAG level in malarial infected patients is based on the findings of higher requirement of lipids for the growth of the parasite which *de novo* synthesis by the parasite might not meet completely. Incidentally, lipids are synthesized in the liver which happens to be the major site for *Plasmodium* infection (Vial *et al*., 2003) and this raises

Table 2: Levels of glucose and TAG in malarial infected subjects

| | Age group (year) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 0-15 | | 16-30 | | 31-35 | | 46-60 | |
| Parameters | M | F | M | F | M | F | M | F |
| **Changes in serum glucose (mmol $L^{-1}$)** | | | | | | | | |
| Malarial receiving treatment | 4.00±0.64 | 5.02±0.93 | 4.73±0.48 | 5.6±0.61 | 4.18±0.58 | 4.77±0.84 | 4.76±0.29 | 5.26±0.28 |
| Infected not receiving treatment | 3.95±0.31 | 4.28±0.10 | 3.84±0.58 | 4.24±0.62 | 4.14±0.91 | 4.24±0.59 | 3.78±0.23 | 4.27±0.54 |
| Healthy no malaria infection subjects | 5.30±0.01 | 5.45±0.23 | 5.04±0.60 | 6.10±1.0 | 4.25±0.51 | 5.09±1.0 | 5.03±1.21 | 5.52±0.72 |
| **Changes in serum tag (mmol $L^{-1}$)** | | | | | | | | |
| Malarial Receiving treatment | 1.17±0.38 | 0.90±0.50 | 2.35±0.85 | 2.15±0.74 | 2.17±1.40 | 1.54±1.07 | 1.80±0.89 | 1.26±0.67 |
| Infected not receiving treatment | 1.07±0.29 | 2.17±0.42 | 1.14±0.28 | 1.32±0.50 | 1.09±0.70 | 1.29±1.44 | 1.19±0.13 | 0.92±0.57 |
| Healthy no malaria infection subjects | 1.26±0.51 | 1.09±1.00 | 1.68±1.54 | 2.00±0.60 | 1.50±0.11 | 1.41±0.22 | 1.21±0.28 | 1.96±0.23 |

Results are presented as Mean±SD. M: Male, F: Female

claims to the relationship between lipid synthesis and *Plasmodium* infection in the liver. The augmentational utilization of host nutrients by the *Plasmodium* parasite could contribute to the observed decrease is serum TAG for malaria infected patients. Serum TAG level was evidently higher among the group of malarial infected patients receiving anti-malarial drug treatment. Anti-malarial inhibit parasite action and promote parasite clearance and these reduce the demand on blood lipids causing an increase in the mobilization of lipids to compensate for the energy loss due to parasite activities (Harris, 2006).

Treatment with two different types of anti-malarial drugs increased both serum glucose and TAG more than the level induced by one type of anti-malarial drug (Table 1). The increase in serum glucose induced by the one type of anti-malarial drug was higher when compared with the amount obtained for the infected patients yet to receive treatment, but lower than the values for the healthy (control) subjects. However, for TAG the level induced by either one or two different types of anti-malarial drug was higher than the TAG concentration for either healthy individuals or malarial infected patients yet to receive treatment. Previous studies have shown that treatment with one type of anti-malaria drug such as 4-aminoquinoline raises blood glucose concentration (Smith *et al*., 1987) when compared with those not being treated, hence anti-malarial treated patients who develop hypoglycemia are rare (Fisher, 1983). Chemotherapeutic-induced increase in blood glucose concentration could be based on the influence of some anti-malarial drugs on insulin related activities and glucose homeostasis (Cynober *et al*., 1987). The quinine and quinidin a cinchonal alkaloid are known to increase insulin secretion by blocking ATP-sensitive potassium ($K^+$ ATP) channel in pancreatic beta cells (Fatherazi and Cook, 1991).

Combination of two different types of anti-malarial drug in the treatment of malarial infection could significantly improve the hypoglycaemic risk but it's highly exaggerated influence on serum TAG may be worrisome, especially now that TAG is seriously implicated as a single risk factor of cardiovascular disorder. Post treatment data are therefore required to provide more understanding in order to better advise health care providers.

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