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# Correlates between Changes in Serum Nickel Concentration, Pathogenesis and Symptomatology of Acute *Falciparum* Malaria Infection in Adults

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## ABSTRACT

Serum nickel concentration was measured in 80 adult patients (40 males and females each; age range, 18-40 years) presenting with acute, uncomplicated *falciparum* malaria infection and a control group of 20 age-matched, healthy individuals. Patient selection and pre-qualification was done by simple random sampling of individuals presenting at the Bauchi State Specialist Hospital Outpatient Department with a history of fever and malaise, and who were confirmed to be infected with the *Plasmodium falciparum* malaria parasite by microscopic examination of Giemsa-stained thin blood slides. Changes in mean serum nickel concentrations were assessed using One-Way Analysis of Variance (ANOVA). The method of Least Significant Difference (LSD) was used to further assess the source of the difference in concentrations where the p value for ANOVA was <0.05. The mean serum nickel concentration was 2.00 ± 0.05 µg/dl in healthy individuals. The serum nickel concentrations were found to decrease by 50.0% in both the male and female patients, with each of them having a mean serum nickel concentration of 1.00 ± 0.01 µg/dl respectively, $P < 0.05$. The decreased serum nickel concentration can account for some of the symptoms associated with the acute onset of human *falciparum* malaria infection, particularly the following: muscular discomfort, headache, limb pain, weakness, malaise and decreased serum iron since studies on nickel deprivation in animals have shown similar results. Specifically, changes in mitochondrial function because of decreased serum nickel may be associated with the observed malaise in acute *falciparum* malaria infection. In addition, since studies on animals have shown a perturbation in vitamin B-12 balance due to low serum nickel, the observed decrease in serum nickel during acute falciparum malaria infection can also have a profoundly negative effect on the ability of the human hematopoietic system to synthesize more red blood cells in order to counterbalance the loss due to merozoite-induced haemolysis. This is because of the immense significance of this vitamin in haemotopoiesis. Therefore, this finding suggests a potentially important role for nickel in the pathogenesis of this endemic tropical disease.

**Keywords:** disease, haematopoiesis, health, tropics

## INTRODUCTION

Nickel (Ni), together with the elements boron, silicon, vanadium and arsenic have been described as ultra-trace elements with essential functions in both animal and plant nutrition (Dugger 1983; Nielsen 1988; Anke *et al*. 1988; Hunt 1989; Nielsen 1990, 1991). Although it has been over three decades now since Ni was suggested to be an essential nutrient, a conclusive definition of a biochemical function for this metal in higher animals have been elusive, until work with bacteria, plants and turnicates gave results which could give clues to the nature of the function of Ni in higher animals (Nielsen 1991). Ni is a component of the enzyme urease. Furthermore, several enzymes in both aerobic and anaerobic bacteria are Ni-dependent (Anke *et al*. 1988). Functionally, this metal activates or inhibits several enzymatic reactions, considered crucial in humans and other animals (Schnegg and Kirchgessner 1978). Work on Ni-deficient chicks and rats have indicated the presence of both macroscopic and microscopic changes in the liver of these animals, including abnormalities of the following sub-cellular organelles: rough endoplasmic reticulum and mitochondria, decrease in phospholipids, depressed hematocrits and generally thinner and unhealthier animals (Nielsen and Ollerich 1974; Spears *et al*. 1978). Many of these changes are considered indicative of an essential role for Ni in protein synthesis in animals. Ni deficiency studies in rats also exhibited decreased growth, low hemoglobin count, low serum urea, adenosine triphosphate (ATP), glycogen, triglycerides and a decrease in the activity of several liver and kidney enzymes (Uthus and Poellot 1996). This metal also plays an interactive role with other minerals necessary for the proper biological functioning of various metabolic systems. Specifically, Ni deprivation in rats affects vitamin B-12 levels, with concomitant changes in growth, kidney-to-bodyweight ratios and plasma concentration of Ni, iron and molybdenum (Uthus and Poellot 1996). In this study, we measured the serum concentration of Ni in adult patients presenting acute *falciparum* malaria infection since some of the consequences of the pathogenic outcomes and the accompanying symptomatology of this endemic tropical disease are similar to those reported in Ni deprivation studies in rats. The most notable among them is general malaise and low hematocrit and changes in serum iron concentration (Buyse *et al*. 1996; Griffiths *et al*. 2001).

## SUBJECTS AND METHODS

### Study design

Patient selection and pre-qualification was done by simple random sampling of individuals presenting at the Bauchi Specialist Hospital Outpatient Department with a history of fever and malaise within a period of 1-8 days, and who were confirmed to be infec-

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ted with the *falciparum* malaria parasite by microscopic examination of Giemsa stained thin blood slides. All the patients were found to present moderate parasitaemia, with parasite density in range of 1000-10,000 asexual forms / ml of blood.

Patients presenting concomitantly with any of the following illnesses: liver diseases, anaemia, alcoholism, metabolic bone disease, protein energy malnutrition, acute *falciparum* malaria infection greater than eight days were excluded in this study. Similarly, patients with a history of self-medication within the prescribed period of acute infection (day 1-8) were also not enrolled in this study. Based on these criteria a total of 80 patients comprising of 40 males, 40 females were enrolled in the study. The control group was made up of 20 healthy male and female adults. The age range for both the patients and the control group was 18-40 years.

## Collection and Preparation of Serum Samples

Blood samples were collected between the hours of 9.00 a.m. and 11.00 a.m. by venepuncture of the antecubital vein into clean, sterile, plastic centrifuge tubes. The samples were centrifuged at 3000 × *g* for ten minutes after clotting. Sera was collected by aspiration using a Pasteur pipette and assayed within 24 hours.

## Assay for serum Ni concentration

The concentration of nickel in serum was determined using Buck Scientific Atomic Absorption Spectrophotometer (AAS) VPG System, Model 210 (Buck Scientific Corporation, California, U.S.A.). Serum samples were digested using a mixture of nitric and perchloric acids. 0.5 ml of serum was mixed with 5 ml nitric acid and 2 ml perchloric acid. The mixture was heated for 2 hours at 100°C. The resulting clear, colourless sample at the end of the digestion was indicative that all carbonaceous materials have been combusted via the digestion process. After cooling, the digest was made up to 25 ml with doubly distilled, deionised water and used for the Ni determination as follows:

Nitric acid (0.1 M) was aspirated for 30 seconds and then the absorbance of the instrument zeroed. After that, the absorbance for both standard and serum sample solutions were measured in triplicate readings, with aspiration of 0.1 M nitric acid for 10 seconds after each reading to clean the burner.

## Statistical Analysis

Data analyses were effected using MINITAB-10 Statistical Software. Comparison of mean serum Ni concentration between the control group and patients were done using one-way analysis of variance (ANOVA). Where P values were $< 0.05$, the Least Significant Difference (LSD) was used to test for the difference between pair of means. P values $< 0.05$ were considered significant.

## Ethics

This work was conducted in accordance with the following ethical declarations: World Medical Association's Declaration of Helsinki (1996), World Medical Association's Declaration of Lisbon on the Rights of the Patient (1995), CIOMS/WHO International Guidelines for the Conduct of Research Involving Human Subjects (1993).

## RESULTS AND DISCUSSION

The results obtained are shown in **Table 1**. The serum Ni concentration in the control was found to be 2.00 ± 0.05 µg/dL. Among the *falciparum* malaria patients, the serum Ni concentration was 1.00 ± 0.01 µg/dL. Relative to the control serum concentration, the serum Ni levels in the patients was significantly lower, $P < 0.01$.

During the life cycle of the *falciparum* malaria parasite in its human host, the lance-shaped sporozoites injected when the mosquito takes a bite invade the liver cell parenchyma where they multiply asexually (Miller *et al*. 2002; Garba and Gatsing 2007). Eventually merozoites are released into the circulation as a consequence of a series of transformations accompanying sporozoite invasion of the liver (Bruce-Chwatt 1985). These merozoites then invade the host red blood cells leading to the lysis of both the infected and uninfected erythrocytes (Williamson *et al*. 1996). Red cell haemolysis is one of the most important determinants of the pathogenic outcomes of this disease (White and Ho 1992). Accompanying this event is the release of toxic malaria-derived waste products, a perturbation in patient iron status and associated anaemia and a perturbed antioxidant defense status (Molineaux 1996). In terms of symptomatology, the sum aggregate of these events are seen in the patient in the form of lethargy, loss of appetite, and general malaise (Buyse *et al*. 1996). Based on the earlier observations on Ni-deficiency studies indicating the association of low serum Ni with decreased energy metabolism (Nielsen and Ollerich 1974; Spear *et al*. 1978) the low serum Ni observed among *falciparum* malaria patients can be a disposing factor to the general malaise and lethargy associated with this infection. This assertion can be buttressed by taking in view the central role of haemoglobin in energy metabolism. Both glycolysis and oxidative phosphorylation are dependent on adequate oxygen delivery to tissues by red blood cells. A synergism between *falciparum*-induced red cell haemolysis and decreased serum Ni concentration can lead to a significant drop in oxygen delivery to tissues and promote the anaemic state (Abdallah *et al*. 1980; Geelhoed *et al*. 2001). In addition, the drop in vitamin B-12 levels associated with low serum Ni is capable of compounding the symptomatic and clinical picture in this infection since the vitamin is essential for effective erythropoiesis, necessary to replenish the population of red blood cells destroyed during erythrocytic merogony. Furthermore, based on the interactive role of Ni with other minerals in maintaining the proper biological function of metabolic systems, its low levels could affect red cell membrane integrity and enzymatic anti-oxidant defense capability of the human host since both events are dependent on proper metal ion balance and interaction.

**Table 1** Serum nickel concentration in adult male and female *falciparum* malaria patients and control.

| Subjects | n | Mean serum nickel (µg/dL) |
|---|---|---|
| Control | 20 | 2.00 ± 0.05 *, a |
| Male patients | 40 | 1.00 ± 0.01 *, b |
| Female patients | 40 | 1.00 ± 0.01 *, b |

* Significant at $p < 0.01$ (ANOVA)
a, b Significant at $p = 0.01$ (LSD)
b, b Not significant.

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