Original Article

Elevated adiponectin but varied response in circulating leptin levels to *falciparum* malaria in type 2 diabetics and non-diabetic controls

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**Abstract**

*Background:* To investigate effects of *falciparum* malaria on circulating levels of leptin and adiponectin in type 2 diabetes mellitus (T2DM) and non-diabetic controls in relation to measures of adiposity.

*Methods:* Levels of leptin and adiponectin were measured in 100 type 2 diabetics and 100 age-matched controls before and during *falciparum* malaria in a 2-year prospective study. Also, waist circumference (WC), weight, height and hip circumference were measured. Body mass index (BMI) and waist-to-hip ratio (WHR) were computed.

*Results:* At baseline, diabetics had significantly (*p* < 0.05) higher WC and BMI but lower WHR, leptin and adiponectin levels. Baseline leptin correlated positively with WC (*r* = 0.63; *p* < 0.001) and BMI (*r* = 0.63; *p* < 0.001) in diabetics but only BMI (*r* = 0.562; *p* < 0.001) in non-diabetic controls. Baseline leptin and adiponectin correlated positively (*r* = 0.249; *p* = 0.029) in non-diabetic respondents only. Adiponectin correlated negatively with WC (*r* = −0.58; *p* = 0.006) in diabetic males only. During malaria, mean levels of leptin and adiponectin were comparable (*p* > 0.05) between diabetics and controls. However, compared to baseline levels, significant (*p* < 0.001) elevation of adiponectin was found in both study groups. In respect of leptin, significant (*p* < 0.001) rise but decline was observed in diabetics and controls respectively. Malaria-induced leptin correlated negatively with adiponectin (*r* = −0.694; *p* < 0.001) in non-diabetic controls only.

*Conclusion:* Diabetics and controls exhibited increased adiponectin levels due to *falciparum* malaria but differed in response in terms of leptin levels.

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At a glance commentary

Scientific background on the subject

Little is known regarding how leptin and adiponectin respond to infectious agents. With sub-Saharan Africa shouldering over 80% of global malaria burden and predicted to accommodate the highest burden of T2DM by 2030, investigating the response of these adipocytokines to malaria and implications of its interaction with T2DM is paramount.

What this study adds to the field

Falciparum malaria increased cardiovascular disease (CVD) risk of diabetics and non-diabetic controls through elevation of adiponectin levels independent of adiposity. In terms of leptin, elevation and reduction in levels were observed in diabetics and control respondents respectively suggesting different mechanisms for malaria-induced CVD risk in the study groups.

Materials and methods

Study site, participants’ selection, anthropometry and laboratory analyses

The study was carried out at Cape Coast Teaching Hospital (CCTH). CCTH is a referral hospital for the various health facilities in the Central region with a recognized Diabetic Clinic. Cape Coast, the capital of the Central region has an estimated population of 169,894 according to the 2010 Population and Housing Census. The inhabitants are mainly farmers and fishermen in the informal sector with a relatively small proportion of the working population in the formal sector. The metropolis is christened the educational hub of Ghana. Due to its strategic location, characteristics of individuals who patronize the services of CCTH reflect those of the entire region.

One hundred diabetic participants aged 40–80 years were randomly selected from database of diabetics receiving appropriate treatments at the CCTH. Controls were age-matched with the diabetics and were selected from the general inhabitants of the metropolis. In all, 200 respondents who met the inclusion criteria were enrolled for the study. Both groups of participants were followed over a period of two years for symptomatic P. falciparum infection. Anthropometric indices, fasting serum leptin and adiponectin levels were measured before and during P. falciparum malaria. Details of sample preparation and storage have been described elsewhere [21].

Anthropometric measurements

Weight was measured to the nearest 0.1 kg with height to the nearest 0.1 cm. Body mass index was computed as the ratio of weight in kilogramme to the square of the height in metre (kg/m²). Weight and height were measured in light clothing without footwear.
Waist circumference was measured in centimetres with an inflexible tape measure at the midpoint between the lower margin of the last rib and the top of the iliac crest [22]. In terms of hip circumference, it was measured around the widest portion of the buttocks. Waist-to-hip ratio was then computed by dividing waist circumference by the hip circumference.

**Laboratory analyses**

Serum leptin and adiponectin levels were determined by commercially available sandwich enzyme-linked immunosorbent assay (ELISA) kits procured from Assaypro, USA (Assaypro Inc., USA). The detection limits for leptin and adiponectin were 0.12 ng/ml and 0.7 ng/ml respectively. Their respective inter-assay and intra-assay coefficients of variation were 4.5% and 7.2% for leptin and 4.3% and 7.2% for adiponectin.

**Malaria diagnosis**

Malaria was diagnosed by the CareStart™ Malaria HRP2 Pf rapid diagnostic test (RDT) kit (Access Bio Inc., USA). This RDT has been assessed comprehensively to be very sensitive and specific for *P. falciparum* diagnosis and strongly correlates with microscopy [23].

**Ethical approval**

Ethical approval for the study was granted by the Committee on Human Research, Publications and Ethics of the Kwame Nkrumah University of Science and Technology, School of Medical Sciences and Komfo Anokye Teaching Hospital, Kumasi. The study was conducted in accordance with the ethical standards of the CCTH and the World Medical Association declaration of Helsinki. In addition, written informed consent was obtained from all participants.

**Data analysis**

Data analysis was done by the SPSS software version 17. Results are presented as mean ± standard deviation (SD). Mean baseline anthropometric, leptin and adiponectin levels between study groups or sexes were compared by 2-tailed independent sample t-test. The mean levels of the measured parameters before and during malaria were compared across groups by one-way analysis of variance (ANOVA) with Tukey’s posthoc HSD test. Bivariate correlation, simple and stepwise linear regression tests were applied. In all analyses, a p-value <0.05 was considered statistically significant.

**Results**

Baseline anthropometric indices, leptin and adiponectin levels are depicted in Table 1. Diabetics had significantly (p < 0.05) higher WC and BMI but lower WHR, baseline leptin and adiponectin levels (Table 1). Stratification of data by gender showed that diabetic males had comparable (p > 0.05) mean WC, hip circumference and BMI but lower (p < 0.05) baseline mean values for WHR, leptin and adiponectin than their control male counterpart (Table 1). With respect to the female respondents, diabetics exhibited comparable mean hip circumference and WHR with their non-diabetic female counterpart but higher BMI and WC (Table 1).

However, mean baseline leptin and adiponectin levels were lower in diabetic females compared with their non-diabetic female counterpart (Table 1). In each study group, the females exhibited higher (p < 0.05) values for all the measured anthropometric indices than their male counterparts except BMI which was comparable (p > 0.05) between genders, and WHR which was lower (p < 0.05) in females than males in the control group (Figs. 1 and 2). In terms of levels of adipocytokines, diabetic and non-diabetic females had higher baseline mean leptin levels than their respective male counterparts but levels of baseline adiponectin were comparable (Figs. 1 and 2).

In the presence of *P. falciparum* malaria, mean serum leptin levels increased appreciably (p < 0.001) to about ten times the baseline levels for diabetic respondents. In the control group, malaria-induced mean serum leptin level was almost four times the mean baseline value (Table 2). Interestingly, the significantly (p < 0.001) higher levels of leptin and adiponectin in controls than diabetics seen at baseline could not be maintained in the presence of *falciparum* malaria.

Baseline leptin level correlated positively with both WC (r = 0.633; p < 0.001) and BMI (r = 0.63; p < 0.001) in diabetics but only BMI (0.562; p < 0.001) in non-diabetic controls. In addition, baseline leptin and adiponectin correlated positively

| Table 1 – Anthropometric indices, leptin and adiponectin levels of respondents before malaria. |
|---------------------------------|--------------------|--------------------|--------|
| Index                          | Diabetic (N = 100) | Non-diabetic (N = 100) | p-value |
| WC (cm)                        | 99.06 ± 11.4       | 92.81 ± 11.3        | 0.002*  |
| Hip (cm)                       | 105.24 ± 11.31     | 103.11 ± 11.11      | 0.343   |
| WHR                            | 0.90 ± 0.07        | 0.95 ± 0.07         | <0.001* |
| BMI (kg/m²)                    | 28.50 ± 4.65       | 26.09 ± 5.34        | 0.025*  |
| Leptin (ng/ml)                 | 21.24 ± 4.07       | 191.51 ± 24.20      | <0.001* |
| Adiponectin (mg/ml)            | 2.5 ± 0.31         | 5.09 ± 0.51         | <0.001* |

### Male respondents (N = 32) (N = 26)

| WC (cm) | 91.69 ± 11.24 | 89.33 ± 10.92 | 0.409 |
| Hip (cm) | 97.61 ± 11.03 | 96.41 ± 10.90 | 0.666 |
| WHR | 0.86 ± 0.08 | 0.99 ± 0.09 | <0.001* |
| BMI (kg/m²) | 25.50 ± 3.19 | 24.64 ± 1.19 | 0.488 |
| Leptin (ng/ml) | 7.57 ± 0.50 | 116.52 ± 23 | <0.001* |
| Adiponectin (mg/ml) | 2.36 ± 0.32 | 4.96 ± 0.12 | 0.003* |

### Female respondents (N = 68) (N = 74)

| WC (cm) | 102.85 ± 1.13 | 93.86 ± 1.14 | <0.001* |
| Hip (cm) | 108.59 ± 1.10 | 105.17 ± 1.13 | 0.113 |
| WHR | 0.92 ± 0.07 | 0.93 ± 0.06 | 0.316 |
| BMI (kg/m²) | 30.93 ± 1.22 | 25.94 ± 1.22 | <0.001* |
| Leptin (ng/ml) | 38.28 ± 23.33 | 241.05 ± 22.41 | <0.001* |
| Adiponectin (mg/ml) | 2.49 ± 0.21 | 5.20 ± 0.12 | <0.001* |

Figures represent mean ± standard deviation; Abbreviations: BMI; body mass index; WHR: waist-to-hip ratio; WC: waist circumference; N: number of respondents; *: significant p-value.
(r = 0.249; p = 0.029) in non-diabetic respondents only. Intragroup gender-based analysis of data showed a positive correlation of baseline leptin with BMI (r = 0.539; p < 0.001) and WC (r = 0.655; p < 0.001) in diabetic females respondents. In diabetic males, baseline leptin correlated positively with BMI (r = 0.449, p = 0.028), but adiponectin correlated negatively with WC (r = −0.58; p = 0.006). In the control group, baseline leptin correlated positively with BMI in both males (r = 0.658; p < 0.001) and females (r = 0.466; p < 0.001) but WC (r = 0.489; p = 0.029) in males only.

In a stepwise regression analysis, BMI and baseline adiponectin emerged as the independent predictors of baseline leptin levels in non-diabetic respondents with the module accounting for approximately 45% of the observed variation (R² = 0.457, adjusted R² = 0.445; p < 0.001). With respect to the diabetic group, BMI was the only significant independent predictor of baseline leptin level. The module could explain just 35% of the observed variation (R² = 0.36, adjusted R² = 0.351; p < 0.001) in baseline leptin level.

As expected, the various indices of anthropometry correlated positively with each other with an average correlation coefficient of 0.8 observed between WC and BMI in both study groups irrespective of malaria. In the presence of malaria, leptin correlated negatively with adiponectin in non-diabetic controls (r = −0.694; p < 0.001) only. No association was observed between malaria-induced leptin or adiponectin levels and the various measures of anthropometry.

Discussion

Three measures of anthropometry were employed in this study to ascertain the relationship among them and other measured parameters. The observed trend of higher BMI and WC for diabetics than control seems to support previous reports that strongly linked higher values of these parameters of adiposity to T2DM although the specific threshold differed with population [24–30].

In a large multiracial study to define BMI thresholds above which T2DM could be diagnosed for different racial groups in Canada, Chiu et al. reported a value of 26 kg/m² for respondents of the black race [29]. Despite the acknowledged probable differences in characteristics between respondents in the current study and those of Chiu et al., the observed mean BMI for control respondents in the current study
appears to support the findings of the Canadian study [29]. Further stratification of data into gender rather showed that the mean BMI of the control females was closer to the threshold than their male counterpart although the difference between them was not significant. With the mean BMI of diabetic males approaching the 26 kg/m² threshold, that of their female counterpart fell within the obesity category as reported in previous studies [25,31]. This female-related obesity observed in the current study could be ascribed to the positive perception of elderly females to weight gain in the Ghanaians society [32].

Recently, Frank et al. demonstrated that measures of central obesity rather than general obesity were strongly linked to T2DM in the Ghanaians population although the specific index differed with gender [33]. They observed the strongest association between diabetes and WHR with cutoff values of 0.88 and 0.90 reported for females and males respectively [33]. However, the observed mean WHR for male and female respondents in the present study appears inconsistent with the gender-specific thresholds reported by Frank et al. [33] This variation in gender-based WHR values between the current study and that of Frank et al. could be due to differences in sample size, age strata and lifestyle of respondents as earlier reported [33,34].

Interestingly, BMI rather correlated strongly and positively with WC in the current study in support of earlier reports [28,35,36]. These measures of adiposity also correlated positively with leptin, an important adipocytokine known to play a central role in adipose tissue metabolism [5,37]. This positive association of baseline leptin level with the measures of adiposity reinforces the adipogenic role of leptin irrespective of underlying health condition in respondents of the current study [5].

Leptin is known to circulate at very low levels in lipodystrophies but high levels in obese and T2DM individuals suspected of being resistant to the molecule [38,39]. The ideal leptin level in humans differs with study, age, gender and race with consensus on possible reference levels yet to be reached by the scientific community [40–42]. In the present study, baseline mean leptin level was higher for controls than diabetics and in females than the males. Although the gender-specific variation in leptin level has been reported and ascribed to gender variation in body composition, the magnitude of the disparity in the current study suggests possible additional factors such as treatment effect [41]. Indeed, the popular anti-diabetic drug, metformin, has long been found to reduce circulating leptin levels although the extent of reduction may vary with gender [43]. To this end, the huge disparities in baseline leptin levels between diabetics and controls in the current study could be ascribed to possible effect of metformin. On the other hand, the relatively high levels of baseline leptin obtained, especially, in the control group could be an indication of a possible leptin resistance reported in the Ghanaians society [25,44]. This view appears to be further supported by the positive correlation observed between baseline leptin and adiponectin in the non-diabetic control group only, suggesting that, the two hormones seem to exhibit positive feedback relationship instead of the expected negative regulatory response to each other. In a number of large sample longitudinal studies, high leptin levels persistently predicted increased risk of T2DM development in males but not females, a finding that appears to suggest that males in the control group of the current study could be at increased risk of developing T2DM compared to their female counterpart [45–47]. This relative protection of females from the negative effect of relative hyperleptinaemia could be due to the male’s higher tendency to develop central obesity compared with the female’s general obesity. With *falciparum* malaria, leptin level in diabetics surged almost ten times the baseline value with that of the controls declining to about 66% of baseline level. These varied responses to leptin levels of the two study groups to *falciparum* malaria may imply varied consequences for the two groups. Although the observed increase in leptin level due to malaria in diabetic respondents seems to be in line with a number of

Table 2 – Analysis of variance comparison of mean leptin and adiponectin levels of respondents before and during malaria.

| Parameter | Diabetic | Non-diabetic | F-value | p-value |
|-----------|----------|--------------|---------|---------|
| | DM (N = 70) | BM (N = 100) | DM (N = 30) | BM (N = 100) |
| WC (cm) | 99.03 ± 11.34 | 99.06 ± 11.41 | 92.79 ± 11.36 | 92.81 ± 11.31 | 16.58 | <0.001* |
| Hip (cm) | 105.19 ± 11.29 | 105.24 ± 11.31 | 103.09 ± 11.13 | 103.11 ± 11.11 | 1.321 | 0.312 |
| WHR | 0.91 ± 0.05 | 0.90 ± 0.07 | 0.94 ± 0.06 | 0.95 ± 0.07 | 9.35 | <0.001* |
| BMI (kg/m²) | 27.98 ± 4.53 | 28.50 ± 4.65 | 26.01 ± 5.75 | 26.09 ± 5.34 | 10.31 | 0.01* |
| Leptin (ng/ml) | 71.46 ± 7.08 | 7.57 ± 0.50 | 64.45 ± 16.17 | 191.51 ± 24.14 | 38.94 | <0.001* |
| Adiponectin (mg/ml) | 10.70 ± 0.52 | 2.50 ± 0.31 | 10.11 ± 0.58 | 5.09 ± 0.51 | 494.41 | <0.001* |

Tukey’s HSD DM BM F-value DM BM p-value

| WC (cm) | 99.03 ± 11.34 | 99.06 ± 11.41 | 0.68 | 92.79 ± 11.36 | 92.81 ± 11.31 | 0.71 |
| Hip (cm) | 105.19 ± 11.29 | 105.24 ± 11.31 | 0.72 | 103.09 ± 11.13 | 103.11 ± 11.11 | 0.70 |
| WHR | 0.91 ± 0.05 | 0.90 ± 0.07 | 0.47 | 0.94 ± 0.06 | 0.95 ± 0.07 | 0.48 |
| BMI (kg/m²) | 27.98 ± 4.53 | 28.50 ± 4.65 | 0.42 | 26.01 ± 5.75 | 26.09 ± 5.34 | 0.53 |
| Leptin (ng/ml) | 71.46 ± 7.08 | 7.57 ± 0.50 | <0.001* | 64.45 ± 16.17 | 191.51 ± 24.14 | <0.001* |
| Adiponectin (mg/ml) | 10.70 ± 0.52 | 2.50 ± 0.31 | <0.001* | 10.11 ± 0.58 | 5.09 ± 0.51 | <0.001* |

Figures represent mean ± standard deviation; *: significant p-value; DM: During Malaria; BM: Before Malaria; N: number of respondents; BMI: body mass index; WHR: waist-to-hip ratio; WC: waist circumference.
experimental and observational studies, the relative decline in leptin levels observed for the non-diabetic controls is at variance with these studies [48,49]. With hyperleptinaemia found to be an independent risk factor for stroke and a predictor of first myocardial infarction, the observed malaria-induced elevation of serum leptin in diabetic respondents could be suggestive of heighted risk for cardiovascular disease [50,51]. This finding calls for special attention to be given to diabetics who get malaria in order to forestall any cardiovascular incident that may occur. In the case of the non-diabetic controls, the decline leptin level observed during malaria could be attributed to possible suppressive effect of adiponectin as the two hormones correlated negatively in this study group. This implies that *falciparum* malaria seems to rather restore the expected traditional antagonistic relationship between adiponectin and leptin in the control respondents [4,5].

Interestingly, a number of studies have associated high and low levels of adiponectin with diabetes and cardiovascular disease although the specific thresholds differ with study, ethnicity and race [16,52–54]. In comparison with published reports, the observed baseline adiponectin levels were generally low in the current study, corroborating the finding that blacks generally exhibit low levels of this molecule, due probably, to low expression levels [52,53,55]. As expected, diabetics recorded much lower values than their non-diabetic counterparts with no gender-specific variation observed in the two study groups. Although the observed trend of baseline adiponectin levels in the two study groups is in line with those of previous studies, the lack of gender-specific variation in circulating levels in the current study appears to deviate from others that reported higher levels for females [52,53,55–57]. The seeming deviation could be due to the relatively small number of respondents in the current study compared with the previous ones. However, baseline adiponectin exhibited negative correlation with WC only in the diabetic group. In non-diabetic controls, the observed elevated adiponectin level in malaria-infected respondents in the current study could be an indication of increased risk to cardiovascular event in both groups of respondents, reinforcing the need for diabetics who get malaria to be given the needed attention and swift response [16,20,60].

**Conclusion**

Falciparum malaria increased adiponectin levels in adult diabetics and non-diabetic controls independent of measures of adiposity. Malaria-induced elevation of leptin level was found only in the diabetic group. In non-diabetic controls, *falciparum* malaria reduced circulating levels of leptin and reversed the baseline association between leptin and adiponectin. These observations suggest different mechanisms by which the risk of cardiovascular event could increase due to malaria in our study groups.

**Conflicts of interest**

Authors declare no conflict of interest.

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