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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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ARTICLE INFO

Article history:
Received 10 January 2015
Accepted 19 February 2016
Available online 27 October 2016

Keywords:
Falciparum malaria
T2DM
Leptin
Adiponectin
BMI

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 ($r = 0.633$; $p < 0.001$) and BMI ($r = 0.63$; $p < 0.001$) in diabetics but only BMI (0.562; $p < 0.001$) in non-diabetic controls. 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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Peer review under responsibility of Chang Gung University.
http://dx.doi.org/10.1016/j.bj.2016.09.003

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.

In spite of a seeming decline of global malaria cases, the condition still affects millions of people in the world [1]. In the case of type 2 diabetes mellitus (T2DM), a recent International Diabetes Federation (IDF) report suggests continued elevation of incidence of the disease across the various continents of the globe [2]. In both conditions, sub-Saharan Africa contributes over 80% to the reported cases globally, suggesting a possible inevitable coexistence of malaria and T2DM in the same individual; a situation that may pose additional health challenge that ought to be investigated. Leptin and adiponectin are important adipocytokines that have been mostly associated with T2DM and other chronic non-communicable diseases [3,4].

Leptin, a 167-amino acid sequence protein with structural similarities to the cytokine family, has been studied extensively in various conditions since its discovery as a satiety signal in 1994 through positional cloning [5]. It is expressed by various tissues including adipocytes, liver, placenta, ovaries, skeletal muscle, pituitary and stomach [6]. Leptin suppresses food intake and stimulates energy expenditure by interacting with its receptors in the hypothalamic region of the brain [5]. Also, it is involved in the regulation of immune cells, blood cells, pancreatic beta cells, muscle, insulin sensitivity and adipocytes [5,7]. In relation to human disease, leptin has been associated with diabetes mellitus, reduced bone mass, atherosclerosis and cancer [3,8–12].

Adiponectin, discovered in the mid-90s by four different groups, is a 30-kDa monomeric polypeptide of 247 amino acid residues synthesized by white adipose tissue [5]. It improves insulin sensitivity and exhibits anti-atherogenic, anti-inflammatory and anti-diabetic properties [4,13–15]. High or low circulating adiponectin levels has been associated with mortality in apparently healthy elderly cohort [16]. However, in patients suffering from chronic kidney disease, cardiovascular disease or type 2 diabetes, high baseline level of circulating adiponectin has been linked to mortality [17–20]. These observations suggest that the exact impact of these biomolecules depends on their circulating levels and the underlying health condition of the individual.

The pleiotropic roles of leptin and adiponectin make them suitable candidates to be studied under varied disease and health conditions. To this end, leptin and adiponectin have been studied extensively in chronic non-communicable diseases such as diabetes, cancer and cardiovascular disease [4,12,18,20]. However, little is known about how these adipocytokines respond to infectious agents such as the *Plasmodium* parasite and its consequence to cardiovascular health of the affected. With sub-Saharan Africa predicted to shoulder the highest burden of type 2 diabetes mellitus by 2030, it may be important to examine the role that *Plasmodium* infection plays in this context since Africa is responsible for more than 80% of global malaria burden. Therefore, the current study was undertaken to investigate the effects of *Plasmodium falciparum* infection on circulating levels of leptin and adiponectin in T2DM and non-diabetic controls in relation to measures of adiposity in a two-year prospective study.

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/m^2). 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 HRP2Pf 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).

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/m^2)	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/m^2)	25.50 ± 1.19	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/m^2)	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.

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 counterpart 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

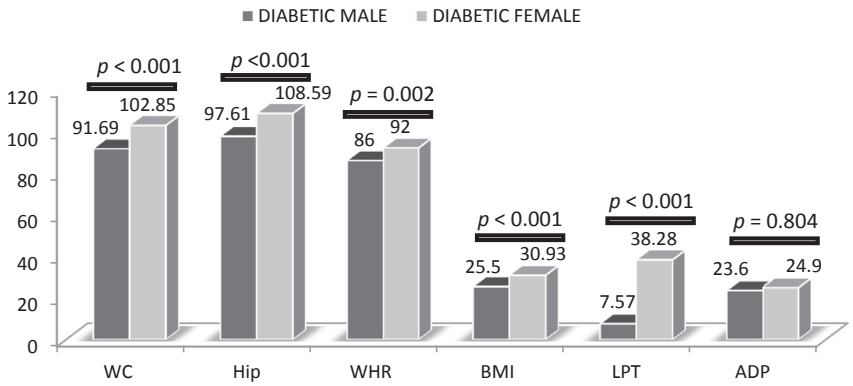

Fig. 1 – Anthropometric indices and levels of selected adipocytokines in male and female diabetics. Abbreviations: WC: waist circumference (cm); Hip: hip circumference (cm); WHR: waist-to-hip ratio $\times 10^{-2}$; BMI: body mass index (kg/m^2); LPT: leptin ng/ml; ADP: adiponectin $\times 10^{-1}$ mg/ml.

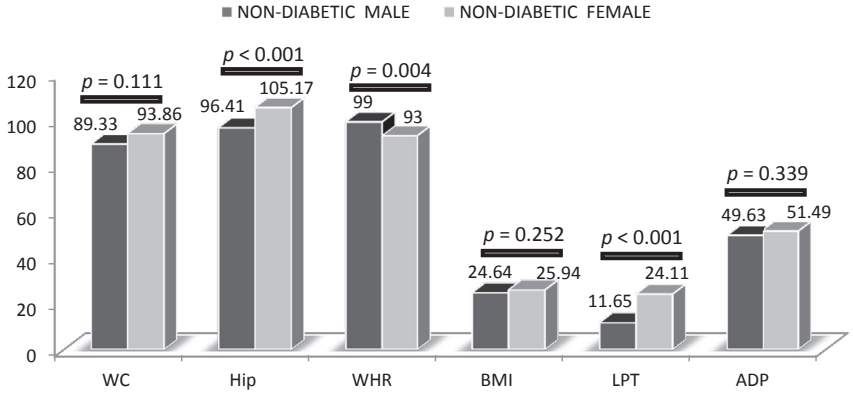

Fig. 2 – Anthropometric indices and levels of selected adipocytokines in male and female controls. Abbreviations: WC: waist circumference (cm); Hip: hip circumference (cm); WHR: waist-to-hip ratio $\times 10^{-2}$; BMI: body mass index (kg/m^2); LPT: leptin $\times$ 10 ng/ml; ADP: adiponectin $\times 10^{-1}$ mg/ml.

($r = 0.249$; $p = 0.029$) in non-diabetic respondents only. Intra-group 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 ($R^2 = 0.457$, adjusted $R^2 = 0.445$; $p < 0.001$). 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 ($R^2 = 0.36$, adjusted $R^2 = 0.351$; $p < 0.001$) 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/m^2 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

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/m^2)	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	P-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/m^2)	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.

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/m^2 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 Ghanaian society [32].

Recently, Frank et al. demonstrated that measures of central obesity rather than general obesity were strongly linked to T2DM in the Ghanaian 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 Ghanaian 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

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 heightened 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 counterpart 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 male gender of the diabetic respondents suggesting that, even in diabetes, the anti-obesity function of adiponectin was preserved but specific for visceral fat accumulation. In addition, this observation reiterates the point that gender-specific variation of adipocytokines must not only be viewed in terms of circulating levels but their relationship with measures of adiposity [58].

Interestingly, *falciparum* malaria elevated drastically, serum adiponectin levels in both study groups contrary to an earlier small sample cross-sectional study of Blümer et al. that did not observe any difference in adiponectin levels between *P. falciparum*-infected and uninfected subjects [59]. Work by Teoh et al. on vascular wall revealed a rise adiponectin level in response to vascular injury, an observation that was explained to indicate advanced atherosclerosis [60]. In addition, a number of recent reports have associated high levels of adiponectin to all-cause mortality in adults [16,20]. Relating results of the current work to these earlier reports, 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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