

# Functional paradox of leptin and adiponectin in diabetes patients and controls in the Cape Coast Metropolis of Ghana

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## ABSTRACT

**Aim:** To investigate the concept of obesity paradox in diabetes patients and nondiabetic control in the Cape Coast Metropolis of Ghana. **Materials and Methods:** Levels of leptin, adiponectin, total antioxidant power (TAP), lipid peroxides, and C-reactive protein (CRP) were assessed in 115 diabetics and an equal number of control respondents. Furthermore, various anthropometric indices and blood pressure were measured using standard methods. Levels of biomarkers were compared between groups based on body mass index or blood pressure classifications. **Results:** Control respondents exhibited higher ( $P < 0.05$ ) levels of leptin, adiponectin, and TAP but lower levels of CRP and peroxides than diabetes patients. In each study group, overweight/obese respondents exhibited higher ( $P < 0.05$ ) leptin level but comparable ( $P > 0.05$ ) mean levels of the various biomarkers, except TAP level which was higher ( $P < 0.05$ ) in the overweight/obese diabetic respondents only. Mean level of adiponectin was lower ( $P < 0.05$ ) only in systolic diabetic hypertensives with comparable ( $P > 0.05$ ) levels of the other biomarkers between diabetes patients and their control counterpart. Irrespective of diabetes, obesity, or hypertensive status, leptin associated positively with various measures of adiposity. Adiponectin correlated positively with leptin ( $R > 0.38$ ;  $P < 0.05$ ) only in the control respondents, suggesting a possible functional paradox of the adipocytokines in this group of respondents. **Conclusion:** Overweight/obese respondents appear metabolically healthier than their normal-weight counterparts. However, further studies are needed for proper understanding of this concept in the Ghanaian context.

**Keywords:** Adiponectin, C-reactive protein, leptin, obesity paradox, total antioxidant power

## Introduction

The health effects of obesity are mediated through the interaction among various biochemical markers such as

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	<b>DOI:</b> 10.4103/MJDRDYU.MJDRDYU_271_16

those of inflammation, oxidative stress, and adipocytokines such as leptin and adiponectin. Indeed, fat accumulation is associated with inflammation and oxidative stress which serve as the main mechanisms through which Type 2 diabetes mellitus and other obesity-associated health conditions are established.<sup>[1,2]</sup> The recognition of metabolic paradox in several obesity-associated health conditions has open the way for other biomarkers to be assessed in the context of overweight, obesity, and normal-weight respondents. Obesity still remains a public health challenge in both developed and developing economies. In Ghana, obesity prevalence increases from rural to urban settings.<sup>[3]</sup> The obesity paradox postulates that certain obese individuals appear to exhibit

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**How to cite this article:** Acquah S, Boampong JN, Eghan Jnr BA. Functional paradox of leptin and adiponectin in diabetes patients and controls in the Cape Coast Metropolis of Ghana. *Med J DY Patil Univ* 2017;10:268-76.

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better prognostic cardiovascular disease risk than their normal-weight counterparts with similar underlying health conditions.<sup>[4-10]</sup> This phenomenon, which was recognized decades ago,<sup>[11,12]</sup> indicates that global fat accumulation *per se* may not be the only major driving force behind the numerous obesity-associated health conditions. Rather, the location of the accumulated fat and its interaction with other metabolic indices may also be important in the reported varied health consequences of obesity. Interestingly, the presence of the paradox in obesity does not in any way suggest that uncontrolled fat accumulation promotes health. Indeed, Arnlöv *et al.*<sup>[2]</sup> demonstrated that irrespective of the presence of metabolic syndrome, fat accumulation increased the risk of individuals to cardiovascular disease. In spite of this observation, the concept of paradox appears to be present in several other chronic diseases.<sup>[4-10,13]</sup> Several factors such as age, cardiorespiratory fitness, body composition, medical treatment, nutritional status, and mortality risk have been cited as important explanations to the observed obesity paradox in several populations.<sup>[14-18]</sup> Scientific information in Ghana, in particular, and the Sub-Saharan Africa, in general, on obesity in relation to the paradox observed in other populations is virtually nonexistent in spite of the acknowledged impact of obesity on her populace currently and in the near future.<sup>[19]</sup> In fact, the 2015 estimates by the International Diabetes Federation suggest that the 14.2 million people living with diabetes in the Sub-Saharan Africa region are expected to rise to 34.2 million people by 2040,<sup>[19]</sup> representing an increase of over 140%, the highest in the world. Obesity has been identified as the major contributor to the predicted increased incidence of diabetes in the region. As a result, it does not come as a surprise that most research works in the Sub-Saharan Africa region tend to focus on the negative effects of obesity with little or no attention to the emerging paradox that has been observed in other populations. Considering the likely effect of the emerging obesity paradox on therapeutic, preventive, and other managerial decisions in relation to health and disease, it may be important to explore the phenomenon in Ghana to allow for targeted decisions aimed at improved management and prevention of diabetes in the country. As a result, the current study was designed to compare the levels of lipid peroxides, total antioxidant power (TAP), C-reactive protein (CRP), leptin, and adiponectin in overweight/obese and normal-weight diabetic and nondiabetic respondents in the Cape Coast Metropolis of Ghana who may be hypertensive or not.

## Materials and Methods

### Study site, selection of study respondents, and laboratory measurements of biomarkers

The Cape Coast Teaching Hospital (CCTH) served as the site for selection of participants, blood sampling, blood pressure, weight, and height measurements. Meanwhile, laboratory determinations of serum levels of TAP, CRP, lipid peroxides, leptin, and adiponectin were carried out at the laboratory of the School of Medical Sciences, University of Cape Coast. CCTH remains the only tertiary hospital for referrals by the various health facilities in the Central Region. It has a well-organized diabetic clinic that manages diabetic patients from the various health facilities within the Cape Coast and other districts of the region. According to the 2010 Population and Housing Census report by the Ghana Statistical Service, the Central Region with an estimated annual population growth rate of 3.1% is one of the fastest growing regions in Ghana. CCTH is located in Cape Coast which serves as the capital of Central Region. Applying the regional growth rate to a population of 169,894 in 2010, Cape Coast is expected to house an estimated 197,918 people by 2015. However, 35.1% of the population is below 18 years of age. The main occupations of majority of the adult population of Cape Coast are farming, fishing, and petty trading in the informal sector with a few in the formal sector of the economy. Generally, the characteristics of inhabitants of the Cape Coast Metropolis reflect those of the entire Central Region.

In all, 230 respondents made up of 115 diabetes patients and an equal number of nondiabetic controls were enrolled in the study. Diabetics were selected at random from a pool of over 1500 registered diabetic patients attending the Diabetic Clinic at CCTH. The nondiabetic controls were selected from the inhabitants of the Cape Coast Metropolis and age-matched with their diabetic counterpart. The study was conducted between November 2011 and December 2013. Details of participants' selection regarding inclusion and exclusion criteria, sample collection, and preparation have been published elsewhere.<sup>[20,21]</sup> Weight, height, body mass index (BMI) computation, waist circumference (WC), hip circumference, and waist-to-hip ratio (WHR) calculation were in strict adherence to the WHO Expert Panel Report of 2008.<sup>[22]</sup> Body adiposity index which is considered as a superior alternative to BMI was computed from height and hip circumference based on a proposed formula by Bergman *et al.*<sup>[23]</sup>

Serum levels of adiponectin, leptin, and CRP were determined by enzyme-linked immunosorbent assay kits following the manufacturer's instructions (Assaypro Inc., St Charles, MO,

USA). TAP and lipid peroxides were measured, respectively, by colorimetric and spectrophotometric techniques in accordance with instructions from the manufacturer (Oxford Biomedical Research, USA).

### Ethical approval

The study received approval from the Committee on Human Research, Publications, and Ethics of the Kwame Nkrumah University of Science and Technology, Kumasi. In addition, every adopted protocol was in strict adherence to the Ethical Standards of CCTH, Ghana Health Service, and the World Medical Association, Declaration of Helsinki. Above all, each study participant provided a written informed consent.

### Statistical analysis

Data were presented as mean ± standard deviation. Diabetics and nondiabetic controls were grouped into two according to the BMI or blood pressure classifications to obtain a total of four groups which were treated as independent samples. Mean levels of the various indices were compared across groups by one-way ANOVA with Tukey Least Significant Difference *post hoc* test. Bivariate Pearson correlation test was applied to investigate linear associations between any pair of measured indices, followed by simple and stepwise regression analyses. Data analysis was conducted by the SPSS version 17 (SPSS Inc., Chicago, USA). In all analyses, a *P* < 0.05 was considered statistically significant.

## Results

This preliminary study involved 230 respondents who were made up of 115 diabetics and 115 nondiabetic controls aged 38–80 years. Each study group was divided into normal-weight (BMI = 18.5–24.9) and overweight/obese group of respondents based on a two-stage BMI classification. Generally, nondiabetic controls had higher (*P* < 0.05) mean levels of leptin, adiponectin, and TAP but lower levels of CRP and peroxides than their diabetic counterpart [*P* < 0.05; Table 1]. In each study group, overweight/obese respondents exhibited higher [*P* < 0.05; Table 1] mean hip circumference and leptin level than their normal-weight counterpart. Mean levels of all the other indices were comparable between normal-weight and overweight/obese respondents in each study group, except the mean levels of TAP and systolic blood pressure (SBP), which were higher [*P* < 0.05; Table 1] in the overweight/obese diabetic respondents only. Comparison of mean levels of measured indices of respondents in each study group using a three-stage BMI categorization, normal-weight (BMI = 18.5–24.9), overweight (BMI = 25–29.9), and obese (BMI ≥30) respondents, yielded similar results as no statistically significant (*P* > 0.05) difference was found between the overweight and obese respondents in respect of any of the measured indices (data not shown).

**Table 1: Levels of biochemical and other anthropometric indices according to body mass index**

Parameter	Diabetes		Nondiabetes		F	P
	≤25 (n=55)	>25 (n=60)	≤25 (n=57)	>25 (n=58)		
Leptin (ng/dl)	0.05±0.003	0.34±0.003	1.11±0.23	2.41±0.23	80.3	<0.001*
Adiponectin (mg/ml)	2.76±0.32	2.40±0.24	5.31±0.11	4.96±0.13	13.42	<0.001*
CRP (ng/ml)	2.40±0.05	4.0±0.03	1.10±0.05	1.92±0.04	5.7	0.001*
TAP (µM)	143.0±4.44	263.76±2.02	271.77±2.02	237.30±1.73	2.68	0.045*
Peroxide (µM)	8.10±0.95	8.72±0.96	4.91±0.78	5.01±0.78	4.78	<0.001*
BAI	33.66±9.35	29.40±8.29	33.19±5.60	32.94±7.42	1.651	0.14
WC (cm)	79.74±28.94	83.78±43.93	79.38±25.26	93.41±26.54	2.269	0.085
Hip circumference (cm)	93.47±8.63	110.35±11.41	97.07±7.18	109.52±9.87	18.12	<0.001*
WHR	0.91±0.06	0.90±0.06	0.94±0.08	0.93±0.06	0.7734	0.534
Systolic	132.11±21.31	142.55±22.21	131.42±24.30	130.10±26.48	2.15	0.004*
Diastolic	81.45±14.10	81.92±10.74	82.33±16.45	81.09±15.49	1.15	0.224
Tukey LSD comparison of means						
	≤25	>25	P	≤25	>25	P
Leptin (ng/dl)	0.05±0.003	0.34±0.003	<0.001*	1.11±0.23	2.41±0.23	<0.001*
Adiponectin (mg/ml)	2.76±0.32	2.40±0.24	0.472	5.31±0.11	4.96±0.13	0.669
CRP (mg/ml)	2.40±0.05	4.0±0.03	0.196	1.10±0.05	1.92±0.04	0.082
TAP (µM)	143.0±4.44	263.76±2.02	0.009*	271.77±2.02	237.3±1.73	0.469
Peroxide (µM)	8.10±0.95	8.72±0.96	0.83	4.90±0.78	5.01±0.78	0.91
Hip circumference (cm)	93.47±8.63	110.35±11.41	0.04*	97.07±7.18	109.52±9.87	<0.001*
SBP	132.11±21.31	142.55±22.21	0.041*	131.42±24.30	130.10±26.48	0.815
DBP	81.45±14.10	81.92±10.74	0.794	82.33±16.45	81.09±15.49	0.852

Figures represent mean±SD.\*Significant. TAP: Total antioxidants power, CRP: C-reactive protein, BAI: Body adiposity index, WHR: Waist-hip ratio, DBP: Diastolic blood pressure, SBP: Systolic blood pressure, WC: Waist circumference, SD: Standard deviation, LSD: Least Significant Difference

In a Pearson bivariate correlation analysis, WC correlated positively with CRP ( $R = 0.379$ ;  $P = 0.047$ ) but negatively ( $R = -0.345$ ;  $P = 0.022$ ) with diastolic blood pressure (DBP) in normal-weight nondiabetic controls. In the same group, adiponectin correlated positively with leptin ( $R = 0.489$ ;  $P = 0.004$ ) but negatively with weight ( $R = -0.473$ ;  $P = 0.006$ ) as hip circumference exhibited a positive correlation with CRP ( $R = 0.435$ ;  $P = 0.021$ ). In subsequent multiple stepwise regression analyses, BMI and adiponectin were the independent predictors of leptin ( $R = 0.72$ ,  $R^2 = 0.518$ , adjusted  $R^2 = 0.493$ ;  $P < 0.001$ ), with the module explaining 49.3% of the observed variation in leptin levels. With adiponectin as the dependent variable, weight and leptin could independently predict adiponectin ( $R = 0.622$ ,  $R^2 = 0.387$ , adjusted  $R^2 = 0.355$ ;  $P = 0.016$ ), with the model accounting for 35.5% of the observed variation in adiponectin levels. CRP level was independently predicted by hip circumference ( $R = 0.392$ ,  $R^2 = 0.154$ , adjusted  $R^2 = 0.132$ ;  $P = 0.011$ ), but the model could explain only about 13% of the observed variation in CRP levels in normal-weight nondiabetic control respondents.

In the overweight/obese nondiabetic control group, leptin correlated positively with adiponectin ( $R = 0.383$ ;  $P = 0.01$ ) and hip circumference ( $R = 0.385$ ;  $P = 0.012$ ) as TAP associated positively with SBP ( $R = 0.341$ ;  $P = 0.034$ ) and WC ( $R = 0.352$ ;  $P = 0.022$ ). However, stepwise regression

analysis revealed hip circumference as the only independent predictor of circulating leptin level ( $R = 0.77$ ,  $R^2 = 0.635$ , adjusted  $R^2 = 0.574$ ;  $P = 0.018$ ), with the model accounting for more than 57% of the observed variation.

With respect to the normal-weight diabetic respondents, Pearson correlational test revealed negative association of adiponectin with WC ( $R = -0.505$ ;  $P = 0.033$ ) and TAP with SBP ( $R = -0.548$ ;  $P = 0.015$ ). However, no variable could independently predict the other.

In the diabetic overweight/obese group, leptin associated positively with WC ( $R = 0.616$ ;  $P < 0.001$ ), hip circumference ( $R = 0.49$ ;  $P = 0.002$ ), and WHR ( $R = 0.298$ ;  $P = 0.047$ ) but negatively with height ( $R = -0.428$ ;  $P = 0.002$ ). In a multiple stepwise regression analysis with leptin as the dependent variable, WC and height emerged as the independent predictors of leptin ( $R = 0.764$ ,  $R^2 = 0.583$ , adjusted  $R^2 = 0.56$ ;  $P = 0.001$ ), with the model explaining 56% of the observed variation in leptin level in this group of respondents.

When respondents were categorized by SBP, it was observed that generally, nondiabetic control respondents showed higher [ $P < 0.05$ ; Table 2] mean levels for leptin, adiponectin, BMI, hip circumference, and DBP but lower level of peroxides, WC, and WHR. In comparison, diabetic systolic hypertensives exhibited higher mean level of

**Table 2: Levels of biochemical and anthropometric indices according to systolic blood pressure**

Parameter	Diabetes		Nondiabetes		F	P
	≤140 (n=55)	>140 (n=60)	≤140 (n=72)	>140 (n=43)		
Leptin (ng/dl)	0.20±0.03	0.26±0.04	1.90±0.25	1.67±0.24	45.17	<0.001*
Adiponectin (mg/ml)	2.77±0.27	1.82±0.24	5.0±0.13	5.34±0.11	16.73	<0.001*
CRP (mg/ml)	3.78±0.04	2.98±0.03	1.43±0.05	1.44±0.05	4.71	0.004*
TAP (µM)	247.91±2.15	184.54±3.64	230.36±1.92	298.54±1.52	1.36	0.259
Peroxide (µM)	7.90±0.98	8.92±0.78	4.81±0.78	5.11±0.78	4.88	<0.001*
BAI	32.75±7.13	33.77±5.31	30.02±8.39	31.03±7.79	1.52	0.13
BMI (kg/m <sup>2</sup> )	26.53±5.82	25.18±4.11	28.91±6.37	30.41±6.71	3.25	0.03*
Hip circumference (cm)	104.79±10.51	101.35±10.63	102.66±12.30	108.91±13.42	4.3	0.009*
WC (cm)	85.93±29.22	89±20.48	59.09±49.43	85.90±39.31	8.96	<0.001*
WHR	0.96±0.07	0.92±0.08	0.91±0.06	0.89±0.09	3.23	0.018*
DBP	77.21±8.66	86.15±8.70	80.48±9.95	91.11±12.54	4.9	<0.001*
Tukey LSD comparison of means						
	≤140	>140	P	≤140	>140	P
Leptin (ng/dl)	0.20±0.03	0.26±0.04	0.35	1.90±0.25	1.67±0.24	0.628
Adiponectin (ng/ml)	2.77±0.27	1.82±0.24	0.017*	5.0±0.13	5.34±0.11	0.696
CRP (ng/ml)	3.78±0.04	2.98±0.03	0.522	1.43±0.05	1.44±0.05	0.974
Peroxide (µM)	7.90±0.98	8.92±0.78	0.301	4.81±0.78	5.11±0.78	0.211
BMI (kg/m <sup>2</sup> )	26.53±5.82	25.18±4.11	0.241	28.91±6.37	30.41±6.71	0.328
Hip circumference (cm)	104.79±10.51	101.35±10.63	0.594	102.6±12.30	108.91±13.42	0.051
WC (cm)	85.93±29.22	89±20.48	0.144	59.09±49.43	85.90±39.31	0.006*
WHR	0.96±0.07	0.92±0.08	0.064	0.91±0.06	0.89±0.09	0.189
DBP	77.21±8.66	86.15±8.70	<0.001*	80.48±9.95	91.11±12.54	<0.001*

Figures represent mean±SD. \*Significant. TAP: Total antioxidants power, CRP: C-reactive protein, BAI: Body adiposity index, WHR: Waist-hip ratio, DBP: Diastolic blood pressure, WC: Waist circumference, BMI: Body mass index, LSD: Least Significant Difference, SD: Standard deviation

DBP [ $P < 0.001$ ; Table 2] but lower [ $P = 0.017$ ; Table 2] level of adiponectin than their normotensive counterpart.

Meanwhile, diabetic systolic normotensives showed positive association of leptin with WC ( $R = 0.668$ ;  $P < 0.001$ ), BMI ( $R = 0.596$ ;  $P < 0.001$ ), hip circumference ( $R = 0.61$ ;  $P < 0.001$ ), and weight ( $R = 0.459$ ;  $P < 0.001$ ) but negative correlation with height ( $R = -0.347$ ;  $P = 0.022$ ). Above all, adiponectin correlated positively with TAP ( $R = 0.317$ ;  $P = 0.038$ ). However, in a multiple stepwise regression analysis, adiponectin, WC, and height emerged as the independent predictors of leptin ( $R = 0.824$ ,  $R^2 = 0.679$ , adjusted  $R^2 = 0.642$ ;  $P < 0.001$ ), with the model explaining 64.2% of the observed variation in leptin level.

In diabetic systolic hypertensives, leptin correlated positively with CRP ( $R = 0.461$ ;  $P = 0.031$ ), weight ( $R = 0.545$ ;  $P = 0.009$ ), TAP ( $R = 0.548$ ;  $P = 0.008$ ), hip circumference ( $R = 0.601$ ;  $P = 0.006$ ), BMI ( $R = 0.672$ ;  $P = 0.001$ ), and WC ( $R = 0.773$ ;  $P < 0.001$ ) but negatively with height ( $R = -0.571$ ;  $P = 0.006$ ) and adiponectin ( $R = -0.464$ ;  $P = 0.029$ ). A multiple stepwise regression analysis results indicated that adiponectin and WC were the only independent predictors of leptin ( $R = 0.899$ ,  $R^2 = 0.808$ , adjusted  $R^2 = 0.779$ ;  $P = 0.001$ ), with the model accounting for 77.9% of the observed variation in leptin level.

With respect to systolic normotensive nondiabetic control respondents, positive association of leptin with weight ( $R = 0.34$ ;  $P = 0.011$ ), BMI ( $R = 0.482$ ;  $P < 0.001$ ), hip circumference ( $R = 0.538$ ;  $P < 0.001$ ), and adiponectin ( $R = 0.476$ ;  $P < 0.001$ ) was observed. Furthermore, CRP correlated positively with BMI ( $R = 0.295$ ;  $P = 0.03$ ) and hip circumference ( $R = 0.321$ ;  $P = 0.023$ ). Above all, BMI and adiponectin independently predicted leptin level ( $R = 0.724$ ,  $R^2 = 0.524$ , adjusted  $R^2 = 0.493$ ;  $P < 0.001$ ) in this group of respondents, with the model explaining 49.3% of the observed variation in leptin level.

Interestingly, in systolic hypertensive nondiabetic controls, leptin exhibited a positive association with weight ( $R = 0.52$ ;  $P = 0.013$ ), BMI ( $R = 0.642$ ;  $P = 0.001$ ), and hip circumference ( $R = 0.523$ ;  $P = 0.015$ ) although BMI was the only independent predictor of leptin ( $R = 0.657$ ,  $R^2 = 0.432$ , adjusted  $R^2 = 0.388$ ;  $P = 0.008$ ), with the model explaining 38.8% of the observed variation in leptin level.

Categorization of respondents by DBP revealed generally similar results [Table 3] as obtained for systolic categorization between diabetic respondents and nondiabetic control respondents in respect of levels of the various indices. Nonetheless, diastolic hypertensive diabetics had lower [ $P < 0.05$ ; Table 3] BMI and hip circumference but

**Table 3: Levels of biochemical and anthropometric indices according to diastolic blood pressure**

Parameter	Diabetes		Nondiabetes		F	P
	≤90 (n=70)	>90 (n=45)	≤90 (n=76)	>90 (n=39)		
Leptin (ng/dl)	0.22±0.04	0.22±0.042	1.88±0.26	1.57±0.19	44.6	<0.001*
Adiponectin (mg/ml)	2.39±0.27	2.50±0.21	5.07±0.13	5.22±0.11	14.15	<0.001*
CRP (mg/ml)	3.74±0.03	2.11±0.07	1.46±0.04	1.28±0.08	5	0.003*
TAP (µM)	234.05±2.71	165.84±2.24	240.77±1.87	290.54±1.63	0.76	0.52
Peroxide (µM)	8.22±0.70	8.62±0.78	4.60±0.39	5.32±0.51	4.96	<0.001*
BAI	32.87±7.04	33.62±5.32	30.02±8.22	31.50±7.82	1.48	0.18
BMI (kg/m <sup>2</sup> )	26.77±5.76	24.38±3.64	29.43±6.21	30.17±7.29	5.89	<0.001*
Hip circumference (cm)	105.06±10.45	101.19±10.42	105.62±13.55	105.70±12.42	4.23	<0.001*
Waist (cm)	87±28.76	86.71±20.79	67.69±48.97	75.12±43.11	4.12	0.001*
WHR	0.96±0.08	0.93±0.06	0.91±0.07	0.89±0.09	7.56	<0.001*
SBP	125.81±11.04	156.92±14.37	126.51±10.38	152.32±9.88	9.86	<0.001*
Tukey LSD comparison of means						
	≤90	>90	P	≤90	>90	P
Leptin (ng/dl)	0.22±0.04	0.22±0.04	0.997	1.88±0.03	1.60±0.02	0.619
Adiponectin (mg/ml)	2.39±0.27	2.5±0.21	0.893	5.07±0.13	5.22±0.11	0.838
CRP (mg/ml)	3.74±0.03	2.11±0.07	0.78	1.46±0.04	1.28±0.08	0.289
Peroxide (µM)	8.22±0.70	8.62±0.78	0.43	4.60±0.39	5.32±0.51	0.201
BMI (kg/m <sup>2</sup> )	26.77±5.76	24.38±3.64	0.035*	29.43±6.21	30.17±7.29	0.328
Hip circumference (cm)	105.06±10.45	101.19±10.42	0.034*	105.62±13.55	105.70±2.42	0.981
Waist (cm)	87.0±28.76	86.71±20.79	0.962	67.69±48.97	75.12±43.11	0.497
WHR	0.96±0.08	0.93±0.06	0.116	0.91±0.07	0.89±0.09	0.308
SBP	125.81±11.04	156.92±14.37	<0.001*	126.51±10.38	152.32±9.88	<0.001*

Figures represent mean±SD. \*Significant. TAP: Total antioxidants power, CRP: C-reactive protein, BAI: Body adiposity index, WHR: Waist-hip ratio, SBP: Systolic blood pressure, WC: Waist circumference, BMI: Body mass index, LSD: Least Significant Difference, SD: Standard deviation

higher SBP than their normotensive counterpart. Although leptin correlated positively with WC ( $R = 0.772$ ;  $P = 0.042$ ) and BMI ( $R = 0.798$ ;  $P = 0.018$ ) in the diabetic diastolic hypertensive group of respondents, multiple stepwise regression analysis revealed BMI as the only independent predictor of leptin level ( $R = 0.802$ ,  $R^2 = 0.644$ , adjusted  $R^2 = 0.573$ ;  $P = 0.03$ ), with the model explaining 57.3% of the observed variation in leptin level.

In the diastolic normotensive diabetics, leptin associated positively with a number of indices such as WC ( $R = 0.69$ ;  $P < 0.001$ ), weight ( $R = 0.457$ ;  $P < 0.001$ ), BMI ( $R = 0.599$ ;  $P < 0.001$ ), hip circumference ( $R = 0.534$ ;  $P < 0.001$ ), and TAP ( $R = 0.344$ ;  $P = 0.009$ ) but negatively with height ( $R = -0.426$ ;  $P = 0.001$ ). However, WC and height emerged as the only independent predictors of leptin ( $R = 0.764$ ,  $R^2 = 0.583$ , adjusted  $R^2 = 0.56$ ;  $P = 0.001$ ), with the model accounting for 56% of the observed variation.

With respect to the control respondents, nondiabetic diastolic hypertensives exhibited a positive correlation between CRP and BMI ( $R = 0.705$ ;  $P = 0.023$ ). However, weight was the only independent predictor of CRP ( $R = 0.71$ ,  $R^2 = 0.504$ , adjusted  $R^2 = 0.421$ ;  $P = 0.049$ ), with the model explaining 42.1% of the observed variation in CRP levels.

In the nondiabetic diastolic normotensive respondents, leptin correlated positively with WC ( $R = 0.266$ ;  $P = 0.038$ ), weight ( $R = 0.43$ ;  $P < 0.001$ ), BMI ( $R = 0.563$ ;  $P < 0.001$ ), hip circumference ( $R = 0.563$ ;  $P < 0.001$ ), and adiponectin ( $R = 0.46$ ;  $P < 0.001$ ) as height correlated negatively with adiponectin ( $R = -0.284$ ;  $P = 0.023$ ). Meanwhile, BMI and adiponectin were the independent predictors of leptin ( $R = 0.72$ ,  $R^2 = 0.518$ , adjusted  $R^2 = 0.493$ ;  $P < 0.001$ ), with the model accounting for 49.3% of the observed variation in leptin level.

## Discussion

Serum levels of leptin, adiponectin, CRP, lipid peroxides, and TAP have been measured in various disease conditions to assess disease severity, risk of death, or development of a given disease and effectiveness of a given treatment regimen. In the current report, serum levels of the above biochemical indices were compared between normal-weight and overweight/obese diabetic respondents and nondiabetic control respondents who were hypertensive or not, to investigate their relationship with selected anthropometric indices and explore the possibility of metabolic paradox in our setting. In general, the higher level of leptin observed in nondiabetic controls than their diabetic counterpart is in support of a number of previous studies and has been

ascribed to the inhibitory effect of metformin on leptin secretion.<sup>[24-26]</sup> Indeed, metformin has been found to improve sensitivity of cells to leptin action,<sup>[27]</sup> suggesting that the relatively higher leptin levels observed in control respondents of the current study could indicate possible leptin resistance. Interestingly, the observed trend in leptin level in the current study contradicts other previous reports that found higher leptin levels in diabetes patients than controls.<sup>[24,28]</sup> The variation in observation between the current study and the earlier ones<sup>[24,29]</sup> could be ascribed to differences in characteristics of study respondents. For instance, the study by Morteza *et al.*<sup>[24]</sup> compared leptin levels of newly-diagnosed Type 2 diabetes patients with controls whereas that of Pandey *et al.*<sup>[28]</sup> compared obese diabetes patients with normal-weight nondiabetic controls. Indeed, when circulating leptin levels of diabetes patients with longer duration of disease were compared with controls,<sup>[24]</sup> the trend was rather similar to the current report, suggesting that the reduced circulating level of leptin in diabetes patients could probably be a reflection of long-term effect of metformin, although a similar finding in the short-term was reported over a decade ago independent of body weight and fat content in healthy respondents.<sup>[29]</sup> Irrespective of the effect of metformin or diabetes, leptin level was consistently higher in overweight/obese respondents than those with normal weight, further buttressing the view of likely leptin resistance, since leptin is an anti-obesity molecule.<sup>[30]</sup> The positive association of leptin with a number of indices of adiposity, irrespective of diabetes, hypertension, or obesity status, in our sample suggests that the anti-obesity molecule seems to be promoting lipid deposition in respondents of the current report. This lipogenic role of leptin is probably mediated through its interaction with adiponectin as the two molecules correlated positively with each other in the control respondents of the current study. This synergistic relationship between leptin and adiponectin instead of an expected antagonistic association deviates from an earlier study<sup>[31]</sup> and points to a possible functional paradox regarding the two molecules in the nondiabetic control arm of the current study. Meanwhile, the anti-obesity role of adiponectin appeared to be somehow preserved in normal-weight diabetic respondents only as the molecule correlated negatively with weight and WC in this group of respondents. Nonetheless, the comparable level of adiponectin in both weight groups coupled with the synergistic relationship with leptin and a higher TAP level in overweight/obese diabetic respondents raises doubts about the effectiveness of adiponectin's anti-obesity function.

Obesity and inflammation are tightly linked as obesity-induced inflammation underpins the development of several chronic conditions.<sup>[7-10,32]</sup> However, a direct association between CRP

and WC or hip circumference was only observed in control respondents with normal weight, suggesting that increased fat deposition in this group of respondents gives rise to a corresponding increase in inflammation which could be detrimental to cellular function. Ironically, WC correlated positively with TAP in the overweight/obese control respondents. This observation which points to a possible protection of overweight/obese nondiabetic respondents in the current study against obesity-induced oxidative stress is at variance with a number of studies that have associated obesity with oxidative stress and inflammation.<sup>[33,34]</sup> The finding also explains, at least, in part, the comparable levels of CRP and peroxides between normal-weight and overweight/obese respondents in the current study and further positions the overweight/obese group at a metabolically healthier status than their normal-weight counterparts. In the diabetic group, the observed higher level of TAP in overweight/obese respondents of the current study compared with their normal-weight counterparts gives further credence to the improved metabolic status of the overweight/obese respondents of the current study. This metabolic paradox requires further and larger study for better understanding in the Ghanaian context for improved management of obesity-related health conditions.

Hypertension has become a major health challenge for developing and developed countries globally. In Ghana, the condition is highly prevalent in both rural and urban settings and increases with age.<sup>[35]</sup> Hypertension is strongly linked with obesity as it is twice more prevalent in obese individuals compared with the general population and is associated with leptin.<sup>[36-38]</sup> However, mean leptin level did not differ between hypertensive and normotensive respondents of the present study with or without diabetes. This observation which deviates from those of earlier studies<sup>[36,38]</sup> is in support of Imatoh *et al.*<sup>[37]</sup> While the deviation could be ascribed to differences in characteristics such as sample size and apparent health status of study participants between the current study and the earlier ones,<sup>[36,38]</sup> the agreement with the findings of Imatoh *et al.*<sup>[37]</sup> suggests that the mean level of leptin *per se* may not be the only factor driving the development of hypertension in our study. This view is further buttressed by the comparable mean levels of TAP, CRP, and peroxides between normotensive and hypertensive respondents with or without diabetes. As expected, leptin associated positively with the various measures of adiposity, indicating that its effect on hypertension may be mediated through its interaction with adiposity and other adipocytokines such as adiponectin as the two adipocytokines related synergistically in control respondents of the current study with or without hypertension. A direct role of adiponectin in the development of hypertension in the current study was only evident in

systolic hypertensive diabetes patients who had lower mean level of adiponectin than the normotensive counterpart in line with a recent systematic review and meta-analytic study which reported that a rise of 1.64 µg/ml adiponectin level reduces the risk of adult hypertension by 6%.<sup>[39]</sup> Interestingly, control hypertensive respondents exhibited a positive correlation between CRP and BMI, which together with the relationships among leptin, adiponectin, CRP, TAP, and lipid peroxides, and the various measures of adiposity corroborate the reported roles of inflammation, oxidative stress, and adiposity in the pathogenesis of hypertension.<sup>[37,39,40]</sup> Indeed, the exact effect of adiposity on hypertension in the current study differs between diabetes patients and controls depending on the basis of hypertensive classification. In systolic hypertensive controls, WC was significantly higher than normotensives whereas hip circumference and BMI were lower in diastolic hypertensive diabetics than their normotensive counterparts. Although the findings in control nondiabetic respondents corroborate several reports,<sup>[36,41]</sup> that of diabetes patients points to a need for further studies to better understand the phenomenon in the Ghanaian context.

## Conclusion

Overweight/obese respondents appear metabolically healthier than their normal-weight counterpart in spite of comparable levels of most of the measured biochemical indices. Further studies are needed for proper understanding of the concept of obesity paradox in the Ghanaian setting for effective management and prevention of obesity-related health conditions.

## Acknowledgement

We are very grateful to the management of UCC for funding the study. We are also grateful to the study participants, staff, and management of CCTH for the use of their facility for the study. Above all, we are deeply appreciative of the staff and management of UCCSMS, notably those responsible for the multipurpose laboratory for their countless support in ensuring the success of this study.

## Financial support and sponsorship

The study was funded by a research grant from the University of Cape Coast, Ghana.

## Conflicts of interest

There are no conflicts of interest.

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