Assessing the variability and predictability of adipokines (adiponectin, leptin and resistin and their ratios) in non-obese and obese women with polycystic ovary syndrome

CURRENT STATUS: ACCEPTED

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DOI:
10.21203/rs.2.11525/v1

SUBJECT AREAS
Endocrinology & Metabolism  Epigenetics & Genomics

KEYWORDS
Polycystic ovary syndrome, Adiponectin, Leptin, Resistin
Abstract

Objectives
To assess the variability in adiponectin, leptin, and resistin between ovulatory women, and non-obese and obese women with polycystic ovary syndrome (PCOS). The study also explores the ratios of the adipokines and evaluated their predictability for PCOS.

Results
The PCOS group presented with lower adiponectin 13.0(10.49-16.59) vs 18.42(15.72-19.92) µg/ml, p<0.0001, adiponectin: leptin ratio 0.60(0.35-0.88) vs 1.19(0.92-1.37), p<0.0001, and adiponectin: resistin ratio 0.30(0.21-0.43) vs 0.42(0.32-0.62), p<0.0001 but a higher leptin 20.02(14.54-26.80) vs 16.17(14.51-18.36) ng/ml, p<0.0001 and leptin: resistin ratio 0.53(0.37-0.82) vs 0.40(0.27-0.48), p<0.0001 compared to the ovulatory group. The obese PCOS group presented with lower adiponectin 11.04(5.66-13.25) vs 14.18(11.04-18.02) µg/ml, p<0.0001 and 18.42(15.72-19.92) µg/ml, p<0.0001 adiponectin: leptin ratio 0.36(0.27-0.44) vs 0.78(0.61-1.16), p<0.0001 and 1.19(0.92-1.37), p<0.0001 and 0.42(0.32-0.62), p<0.0001 but a higher leptin 26.80(14.28-32.09) vs 17.95(14.86-21.26) ng/ml, p<0.05 and 16.17(14.51-18.36) ng/ml, p<0.0001 and leptin: resistin ratio 0.63(0.46-1.03) vs 0.41(0.30-0.61), p<0.0001 and 0.40(0.27-0.48), p<0.0001 compared to the non-obese PCOS and ovulatory control group, respectively. Adiponectin: leptin ratio presented with the best discriminatory power in predicting PCOS (AUC=0.83) followed by adiponectin alone (AUC=0.79), and leptin: resistin ratio and leptin alone (both AUC=0.69).

Resistin alone presented with the poorest discriminatory power (AUC=0.48).

Introduction
Overweight and obesity are pervasive medical conditions which are considered global
epidemic and threat to public health [1, 2]. A mountain of evidence suggest that obesity is associated with the risk of metabolic diseases such as diabetes mellitus, hypertension, cardiovascular disease, obstructive sleep apnea, various types of cancer and overall mortality [3-5]. There have also been reports of associations between obesity and infertility [6, 7], particularly among women due to the risk of anovulation [1, 8]. Anovulation is a common cause of infertility in women; responsible for not less than 25% fertility problems among couples [9, 10] and 25-50% of female infertility, of which polycystic ovary syndrome (PCOS) accounts over 90% of cases [11].

PCOS is a multisystem, endocrinological, reproductive and metabolic disorder characterized by oligo- and/or anovulation, hyperandrogenism, and polycystic ovaries [12]. Obesity-related adverse alterations in adipose tissue that predispose to metabolic dysregulation has been implicated in PCOS pathogenesis. These adverse alterations include derangements in bioactive cytokines and adipokines such as adiponectin, leptin, and resistin [13, 14]. However, while some studies report comparable adiponectin, leptin and resistin levels [15-17], others report lower adiponectin [18], higher leptin [19] and resistin levels [20] among women with PCOS than healthy controls in relation to obesity.

Thus far, reports regarding the changes in adiponectin, leptin, and resistin in non-obese and obese women with PCOS remain inconclusive. It is possible that differences in geography and its accompanying diversities in genetic and lifestyle characteristics may be involved in the discrepancies observed by previous studies. Additionally, very limited studies have assessed the usefulness of adipokine ratios in predicting PCOS [17, 21]. Sarray et al. [17] recently reported the expediency of adipokine ratio in predicting PCOS. They however indicated that studies in diverse backgrounds to confirm the utility of adipokine ratios as potential biomarkers of PCOS is warranted. In light of this, and the fact
that none of such studies have been conducted to evaluate the validity of the associations in a Ghanaian population, this study aimed at assessing the variability in adiponectin, leptin, and resistin between ovulatory women, non-obese and obese women with PCOS in Ghana. The study also explores the ratios of the adipokines and evaluated their predictability for PCOS.

Materials And Methods

Study Design/Setting

The study was a case-control study. Consecutive consenting women clinically diagnosed of PCOS visiting the Obstetrics and Gynaecology units of Trust Care, Ruma and Asbury were included in the study as cases. PCOS diagnosis was based on the 2003 Rotterdam criteria, in which PCOS diagnosis is confirmed when two of three conditions are met: oligo- and/or anovulation, hyperandrogenism (clinical and/or biochemical), and polycystic ovaries on ultrasound examination [12]. Fertile (eumenorrheic) women visiting the hospital for routine check-up were included as controls. Relevant clinical data of each participant was extracted from the hospital’s archive. Women with Cushing syndrome, hyperprolactinemia, androgen-producing tumors, non-classic adrenal hyperplasia, active thyroid disease, and diabetes were excluded.

Study population and Anthropometric measurements

A total of 52 fertile (ovulatory) and 104 women with PCOS comprising 54 non-obese and 50 obese women were included in this study. The weight was measured in light clothing without shoes, in an upright position using a calibrated analogue scale (Seca, Hamburg, Deutschland). Height was measured without shoes using a stadiometer (Seca, Hamburg, Deutschland). Body mass index (BMI) was calculated using the equation; [BMI = weight/height$^2$ (kg/m$^2$)] [22]. Obesity was defined according to the World Health
Organization (WHO) criteria (BMI ≥ 30 kg/m²) [23]. Waist circumference (WC) and hip circumference (HC) were measured with a measuring tape and waist-to-height ratio (WHtR) = WC (m)/height (m), waist-to-hip ratio (WHR) = WC (m)/HC (m), body adiposity index (BAI) = (100 x HC (m))/(height (m)x√height (m))-18 [24] were calculated.

**Blood sampling, processing and analysis**

Five milliliters of venous blood was obtained from each participant and dispensed into gel separator tubes. The tubes were centrifuged at 1500 x g for 10 minutes at 4 °C to obtain the serum which were stored at -20 °C until analysis. Serum levels of adiponectin, leptin, and resistin were measured based on solid-phase sandwich Enzyme Linked Immunosorbent Assay (ELISA) technique (standardized with an intra- and inter-assay %CVs <10%) (Green Stone Swiss Co Limited, China) according to the manufacturer’s instructions.

**Statistical analysis**

Statistical analysis and graphical presentation was performed using the R Language for Statistical Computing version 3.6.0 (R Core Team, Vienna, Austria) [25]. Chi squared test was used to assess significance of association between the participant characteristics and fertility status. Distribution of adipokines were presented with density plots. Hierarchical clustering by Spearman’s correlation was used to assess relationship between adipokines (and their ratios) with obesity indices. Independent t-test and one-way ANOVA with Tukey test or Mann-Whitney U t-test and Kruskal-Wallis test with Dunn’s test were used to test for significance of difference between groups where applicable. The receiver operating characteristics (ROC) curve analysis was used to evaluate the performance of the adipokines (and their ratios) in predicting PCOS. Confidence was set at 95% and a p value < 0.05 was considered statistically significant.

**Results**
A total of 52 ovulatory women with mean age of 31.63 (±4.88) years and 104 PCOS patients comprising 54 non-obese [mean age=32.11 (±4.25) years] and 50 obese women [mean age= 33.64 (±4.14) years] were included in this study. A higher proportion of the study participants had tertiary education, were employed and did not consume alcohol. A greater number of the control group exercise once/week while the case group rarely exercise. None of the study participant smoked. There was no statistically significant association between fertility status and baseline characteristics (Table 1).

Figure 1. Variability of adipokines and their ratios between ovulatory and PCOS groups. (a, c) Density plots showing distribution of adipokines. (b) Comparison of adipokines and their ratios between case and control groups. Mann-Whitney U test was used to assess significance of difference of adipokines and their ratios between ovulatory and PCOS groups. (d) Comparison of adipokines and their ratios. Kruskal-Wallis H test was used to assess significance of difference of adipokines and their ratios between ovulatory (OC), non-obese (NOP), and obese PCOS (OP) groups. Post-hoc multiple comparisons was by Dunn’s test. ns; not significant, *; significant at p<0.05, **; significant at p<0.0001.

The PCOS group presented with a significantly lower adiponectin [13.0(10.49-16.59) µg/ml vs 18.42(15.72-19.92) µg/ml, p<0.0001], adiponectin: leptin ratio [0.60(0.35-0.88) vs 1.19(0.92-1.37), p<0.0001], and adiponectin: resistin ratio [0.30(0.21-0.43) vs 0.42(0.32-0.62), p<0.0001] but a higher leptin [20.02(14.54-26.80) ng/ml vs 16.17(14.51-18.36) ng/ml, p<0.0001] and leptin: resistin ratio [0.53(0.37-0.82) vs 0.40(0.27-0.48), p<0.0001] compared to the ovulatory group (Fig. 1a & b).

The obese PCOS group presented with a significantly lower adiponectin [11.04(5.66-13.25) µg/ml vs 14.18(11.04-18.02) µg/ml, p<0.0001 and 18.42(15.72-19.92) µg/ml, p<0.0001], adiponectin: leptin ratio [0.36(0.27-0.44) vs 0.78(0.61-1.16), p<0.0001 and 1.19(0.92-1.37), p<0.0001], and adiponectin: resistin ratio [0.24(0.17-0.38) vs 0.40(0.23-0.58),
p<0.0001 and 0.42(0.32-0.62), p<0.0001) but a higher leptin [26.80(14.28-32.09) ng/ml vs 17.95(14.86-21.26) ng/ml, p<0.05 and 16.17(14.51-18.36) ng/ml, p<0.0001] and leptin: resistin ratio [0.63(0.46-1.03) vs 0.41(0.30-0.61), p<0.0001 and 0.40(0.27-0.48), p<0.0001] compared to the non-obese PCOS and ovulatory control group, respectively (Fig. 1c & d).

Figure 2. Correlational analysis and the performance of individual adipokines and their ratios in predicting anovulatory infertility. (a) Correlation among PCOS group. (b) Correlation among ovulatory control group. Hierarchical clustering by Spearman’s correlation was used to assess relationship between adipokines and their ratios with obesity indices. Blue-red coloration represents min (-) to max (+) correlation coefficient. (c) Receiver operating characteristic (ROC) curve was based on binary logistic regression and discriminant classification analysis for PCOS and control groups. †; Test direction is negative (smaller test results indicate presence of condition). A: L ratio; Adiponectin: leptin ratio, A: R ratio; Adiponectin: resistin ratio, L: R ratio; Leptin: resistin ratio.

Among the PCOS group, adiponectin showed a significant negative correlation with BMI (rs=-0.43, p<0.0001), WHtR (rs=-0.36, p<0.0001), BAI (rs=-0.35, p<0.0001), and VAI (rs=-0.19, p=0.049). Leptin had a positive correlation with BMI (rs=0.31, p=0.001), WHtR (rs=0.27, p=0.007), and BAI (rs=0.29, p=0.003). There was no statistically significant correlation between resistin and obesity indices. Adiponectin: leptin ratio showed a negative correlation with BMI (rs=-0.48, p<0.0001), WHtR (rs=-0.38, p<0.0001), and BAI (rs=-0.40, p<0.0001). Adiponectin: resistin ratio presented with similar correlations while leptin: resistin ratio showed a positive correlation with BMI (rs=-0.27, p=0.005) and BAI (rs=-0.29, p=0.003) (Fig. 2a and Table S1). Among the ovulatory controls, adiponectin showed a significantly negative correlation with BAI (rs=-0.33, p=0.017) while resistin showed a positive correlation with WHR (rs=0.31, p=0.028) and WHtR (rs=0.28, p=0.044).
There was no statistically significant correlation between leptin and obesity indices. Adiponectin: leptin ratio had a significant negative correlation with BMI (rs=-0.36, p=0.008) and BAI (rs=-0.39, p=0.004) while adiponectin: resistin ratio showed a significant negative correlation with BMI (rs=-0.29, p=0.038) (Fig. 2b and Table S1). Adiponectin: leptin ratio presented with the best discriminatory power in predicting PCOS (AUC=0.83) followed by adiponectin alone (AUC=0.79), and leptin: resistin ratio and leptin alone (both AUC=0.69). Resistin alone presented with the poorest discriminatory power (AUC=0.48) (Fig 2c).

Discussion
This study reports lower levels of adiponectin, adiponectin: leptin ratio, and adiponectin: resistin ratio but a higher leptin and leptin: resistin ratio among women with PCOS compared to ovulatory controls. Our finding is comparable to a case-control study by Sarray et al. [17], who reported significantly lower levels of adiponectin, adiponectin: leptin ratio, and adiponectin: resistin ratio among women with PCOS compared to healthy controls in Bahrain. A recent study by Baldani et al. also found significantly lower adiponectin and higher leptin among women with PCOS compared to healthy controls in Croatia [26]. Upon stratification of PCOS group by obesity status, we found the obese PCOS group to have a significantly lower adiponectin, adiponectin: leptin ratio, and adiponectin: resistin ratio but a higher leptin and leptin: resistin ratio compared to the non-obese PCOS and ovulatory group, respectively. This finding is in harmony with a case-control study by Olszanecka-Glinianowicz et al. [27] who found serum adiponectin level and adiponectin: resistin ratio to be lowest in the obese PCOS subgroup in comparison with both the normal weight PCOS subgroup and the healthy controls in Poland. In their study, serum resistin levels did not differ significantly between both normal weight and obese PCOS subgroups and the controls which is comparable to our study findings. Studies
by Xiu et al. [28], Arikan et al. [29], and Seow et al. [30] also found similar serum resistin levels among healthy controls, non-obese, obese women with PCOS. Furthermore, Sarray et al. [17] found markedly reduced adiponectin: leptin and adiponectin: resistin ratios among obese women with PCOS compared to non-obese women with PCOS and healthy controls. They also found lower leptin: resistin ratio among obese women with PCOS though not statistically significant. Together with previous findings, our results corroborate the deposition that high body fat indeed play pivotal roles in the pathogenesis of PCOS.

Indeed, evidence suggest that, in women with PCOS, high body fat coupled with dysfunction of adipose tissue results in over-production of adipokines such as leptin and resistin and, the reduced expression of adiponectin. Levels of adiponectin have been shown to decrease in obesity and increase with weight loss [20]. It is considered a ‘beneficial’ adipokine in reproduction [31]. The levels of leptin have been reported to constitutively secreted by adipocytes in proportion to the adipose mass [32]. In obese patients, the levels of leptin are even more elevated due to leptin resistance [33]. Additionally, increased expression of the resistin gene has been observed in human pre-adipocytes, which decreased during adipocyte differentiation. The relationship between resistin and obesity is however convoluted. Whereas some report a direct association [34, 35], others show no significant association with obesity [36-38]. Consistent with these previous reports, we also found that, with the exception of resistin, all other adipokines including their ratios were strongly and more correlated with various obesity indices among women with PCOS compared to the controls. Specifically, adiponectin, adiponectin: leptin ratio, and adiponectin: resistin ratio showed a positive association whereas leptin, and leptin: resistin ratio correlated positively with the obesity indices. This finding is also coherent with studies by Sarray et al. [17] and Golbahar et al. [21].
In order to assess the predictive capabilities of the adipokines and their ratios, we employed the ROC curve analysis with reference to PCOS. We found adiponectin: leptin ratio to have the best discriminatory power in predicting PCOS with an AUC of 0.83. Golbahar et al. also found adiponectin: leptin ratio to have a similarly high discriminatory power with comparable AUC of 0.86 among Bahraini women with PCOS [21]. A much higher discriminatory power (AUC of 0.94) for adiponectin: leptin ratio in predicting PCOS has been reported by Sarray et al. also among women with PCOS in Bahrain [17]. The discrepancies in the predictive power may be attributed to differences in characteristics of the study population, sample size, and methods for biochemical analysis.

Conclusion

This study shows significantly altered serum levels adiponectin and leptin but not resistin in Ghanaian women with PCOS compared to healthy subjects. Obese PCOS patients have the most altered levels of adipokines compared to non-obese PCOS and healthy subjects. Adiponectin: leptin ratio is the best predictor of PCOS compared to individual adipokines.

Limitations

The major limitation of this present study is the relatively small sample size. We recommend the use of larger sample size in future studies.

Abbreviations

PCOS: Polycystic ovary syndrome
BMI: Body mass index
WHO: World Health Organization
T2DM: Type 2 diabetes mellitus
WC: Waist circumference
HC: Hip circumference
WHR: waist to hip ratio
WHtR: waist to height ratio
BAI: body adiposity index
VAI: Visceral adiposity index
ELISA: Enzyme Linked Immunosorbent Assay

Declarations

Ethics approval and consent to participate
Ethical approval for this study was obtained from the committee on Human Research, Publications and Ethics (CHRPE), School of Medical Sciences, Kwame Nkrumah University of Science & Technology (CHRPE/AP/564/17), Ruma Fertility Hospital, Asbury Fertility Hospital and Trust Care Hospital. Written informed consent was obtained from all participants who opted to participate after the aims and objectives of the study had been explained to them. Participation was voluntary, and respondents were assured that the information obtained was strictly for research and academic purposes only and were guaranteed the liberty to opt out from the study at their own convenience.

Consent for publication
Not applicable.

Availability of data and material
The datasets supporting the conclusions of this article are included within the article and its additional file.

Competing interests
The authors declare that they have no competing interests.

Funding
This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.
Authors’ contribution

CO and WKBAO designed the study, supervised the research and laboratory analysis, drafted and revised the manuscript. SAA, EA, EAA and EKAB were involved in the design of the study, collection of data, laboratory analysis, drafting and revision of the manuscript. EWO was involved in the design of the study, collection of data, laboratory analysis, statistical analysis and interpretation, drafting and revision of the manuscript. All authors read and approved the final manuscript.

Acknowledgements

The authors are grateful to the Staff of the Ruma Fertility Hospital, Asbury Fertility Hospital and Trust Care Hospital and all who actively participated in the study.

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Additional File

Additional file 1: Correlation co-efficient and haemodynamic and anthropometric characteristics of the study population.

Table

Due to technical limitations, table 1 is only available as a download in the supplemental files section.

Figures
Variability of adipokines and their ratios between ovulatory and PCOS groups. (a, c) Density plots showing distribution of adipokines. (b) Comparison of adipokines and their ratios between case and control groups. Mann-Whitney U test was used to assess significance of difference of adipokines and their ratios between ovulatory and PCOS groups. (d) Comparison of adipokines and their ratios. Kruskal-Wallis H test was used to assess significance of difference of adipokines and their ratios between ovulatory (OC), non-obese (NOP), and obese PCOS (OP) groups. Post-hoc multiple comparisons was by Dunn’s test. ns; not significant, *; significant at p<0.05, **; significant at p<0.001, ***; significant at p<0.0001.
Figure 2

Correlational analysis and the performance of individual adipokines and their ratios in predicting anovulatory infertility. (a) Correlation among PCOS group. (b) Correlation among ovulatory control group. Hierarchical clustering by Spearman’s correlation was used to assess relationship between adipokines and their ratios with obesity indices. Blue-red coloration represents min (-) to max (+) correlation coefficient. (c) Receiver operating characteristic (ROC) curve was based on binary logistic regression and discriminant classification analysis for PCOS and control
groups. †; Test direction is negative (smaller test results indicate presence of condition). A: L ratio; Adiponectin: leptin ratio, A: R ratio; Adiponectin: resistin ratio, L: R ratio; Leptin: resistin ratio.

Supplementary Files

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Additional file 1.pdf
Table 1.jpg