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Circulating Adiponectin and Resistin Levels Are Associated with Adiposity Indices and Physical Fitness in Healthy Adult Males

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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: The aim of this study was to assess the correlation of physical fitness scores (PFS) with serum adiponectin, resistin, and adiponectin/resistin ratio (AR ratio) in relation to body adiposity indices in healthy adult males.

Material/Methods: This cross-sectional study was conducted at the Clinical Physiology Unit, Physiology Department, King Saud University Medical City, King Saud University, Riyadh, from March 2017 to April 2018. We included 125 healthy adult males. Serum samples were obtained after overnight fasting. Analysis was performed for fasting blood glucose (FBG), glycosylated hemoglobin (HbA1c), basal insulin, lipid profile, resistin, and adiponectin. Bioimpedance analysis (BIA) was used to assess body composition. Based on ideal body composition, PFS were computed as previously published for all subjects and compared with serum markers.

Results: There was a positive correlation of adiponectin with PFS ($r=.218$, $p=0.015$) and an inverse correlation with obesity degree (OD), OD ($r=-.239$, $p=0.001$), body mass index (BMI) ($r=-.244$, $p=0.001$), and waist/hip ratio (WHR) WHR ($r=-.296$, $p=0.001$). Moreover, it was correlated negatively with basal insulin ($r=-.211$, $p=0.009$) and homeostatic insulin resistance model (HOMA-IR) HOMA-IR ($r=-.221$, $p=0.013$). Resistin was correlated negatively with PFS ($r=-.203$, $p=0.023$), while its correlation with OD, BMI, WHR, and HOMA-IR was not significant. AR ratio was positively correlated with PFS ($r=.286$, $p=0.001$) and negatively with OD ($r=-.210$, $p=0.019$), BMI ($r=-.222$, $p=0.013$), WHR ($r=-.308$, $p=0.001$) and basal insulin ($r=-.237$, $p=0.008$). In linear regression analysis, the relationship of PFS was significant with adiponectin ($r=.218$, $p=0.015$), resistin ($r=-.203$, $p=0.023$) and AR ratio ($r=.286$, $p=0.001$). ROC curve analysis showed that individually the values of adiponectin and resistin were not significantly correlated with PFS, but they were significant with the combined AR ratio with AUC 64.6% ($p=0.029$).

Conclusions: Serum adiponectin was positively correlated and resistin was negatively correlated with physical fitness scores based on healthy body composition with low proportion of body adiposity and a higher proportion of fat-free mass. However, the combined effect of adiponectin/resistin ratio is an even better predictor of physical fitness. Moreover, the adiponectin/resistin ratio is even more highly associated with physical fitness than adiponectin or resistin alone.

Keywords: Adiponectin • Body Composition • Body Mass Index • Physical Fitness • Resistin

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Background

Physical inactivity is the fourth leading risk factor for stroke, cardiovascular diseases, and diabetes, with the highest epidemiological impact on general population health globally, as estimated by the Global Burden of Disease Study [1].

The Global Action Plan for Physical Activity and Fitness, initiated in 2018 by the World Health Organization, with the notion of “more active people for a healthier world”, addresses physical activity with a ‘global’ and ‘whole-of-system’ approach for effective promotion of physical activity at the national and subnational levels [2]. Obesity and its repercussions, including cardiovascular disease, cancers, sleep apnea, fatty liver, and knee osteoarthritis, is a major health problem with high risk of morbidity, decreased quality of life, and decreased life expectancy [3]. Adipose tissue not only acts as a depot of energy storage, but also acts a complex endocrine organ that releases certain hormones that play a potential role in the pathogenesis of insulin resistance, type 2 diabetes (T2DM), and obesity [4]. It is well recognized that obesity and, most importantly, visceral adipose tissue accumulation, lead to an increased tendency to develop T2DM [5,6].

Many researchers have identified a substantial list of adipokine proteins, including leptin, adiponectin, resistin, and acylation-stimulating protein, involved in the regulation of glucose, lipid metabolism, and insulin resistance (IR) in obesity and diabetes [7,8]. Therefore, high visceral fat accumulation leading to high insulin resistance is independently related to a prediabetic state and T2DM [9]. Dysregulation of adipose tissue is associated with ectopic fat accumulation in the liver and other abdominal visceral organs [10,11]. Furthermore, it is characterized by a proinflammatory state and adipokine dysregulation along with high IR. All these factors collectively lead to a high risk of T2DM development compared to total body fat mass alone.

Resistin and adiponectin are important adipokines that regulate insulin sensitivity. The cardioprotective adipokine adiponectin, which plays an important protective role in inflammatory mechanisms, increases insulin sensitivity and improves lipid profile, which act together to markedly reduce the atherosclerotic risk in diabetes subjects. Plasma adiponectin concentrations are reported to be decreased in patients with obesity and coronary artery disease (CAD) [12,13]. Resistin is considered an important link between obesity and T2DM since its levels are positively correlated with IR both in vitro and in vivo [14].

Since both adiponectin and resistin have important biological activities in glucose and lipid metabolism, the comparison of the effects of these adipokines on glucometabolic control needs further research. The present study aimed to assess the

correlation of physical fitness scores (PFS) computed from body composition indices with blood circulating levels of adiponectin, resistin, and adiponectin/resistin ratio.

Material and Methods

This cross-sectional study was carried out at the Physiology Department of King Saud University, Riyadh, from March 2017 to April 2018. The Institutional Review Board (IRB) of the College of Medicine, King Saud University approved the study and all subjects signed the consent form for participation in the study. The study adhered to the Helsinki Declaration. We initially recruited 135 subjects from the university staff by convenience sampling technique and the final selection included 125 healthy adult males as per our selection criteria. All participants were healthy individuals with mean age of 40.23 ± 11.62 (range 21-70 years) without any acute or chronic health problems. Individuals with diabetes states, acute renal failure, chronic renal failure, thyroid disease, infections, history of stroke, or steroid intake were excluded. Clinical and demographic data from all participants were recorded on a predesigned form which included waist/hip ratio (WHR), weight, height, and BMI measurements, and exercise habits. Venous blood samples were obtained after 10-12 h of overnight fasting and stored at -80°C . Serum analysis included estimation of fasting blood glucose (FBG), glycosylated hemoglobin (HbA1c), basal insulin, and routine lipid profiles encompassing triglycerides (TGs), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-c), and high-density lipoprotein cholesterol (HDL-c). Moreover, adiponectin and resistin levels were also measured. Human insulin, adiponectin, and resistin immunoassays were carried out by a standard sandwich ELISA technique that used resistin-specific monoclonal antibodies kits from R&D Systems (Abingdon, United Kingdom). The insulin resistance index of the homeostasis model assessment of insulin resistance (HOMA-IR) was determined using the formula $\text{HOMA-IR} = (\text{basal insulin (mU/L)} \times \text{FBG (mmol/L)}) / 22.5$ [15]. A detailed history was taken from the subjects and demographic data were recorded. All patients underwent body composition analysis. Bioelectrical impedance analysis was used to measure body composition with an InBody3.0 (BioSpace, Korea) body analyzer according to the manufacturer's instructions. All assessments were made in the early morning fasting state, wearing light clothing, and after emptying of the urinary bladder [16,17].

InBody 3.0 is an 8-point tactile electrode system (contact with the hands and feet). It has high validity and reliability for estimating body composition for both children and adults in research and clinical settings [18,19]. All participants were directed to wipe and clean their soles with wet tissue and then stand over the foot electrodes for 3-5 min. The machine estimated the following parameters; weight, BMI, obesity degree (OD), body protein, body muscle mass, body fat mass, and body

Table 1. Demographic and clinical data of all study participants.

Variables	Mean	SD	Minimum	Maximum
Age (years)	40.23	11.62	21.00	70.00
Protein mass (kg)	10.94	1.80	6.60	15.60
Fat mass (kg)	23.93	8.50	6.20	52.70
Lean body mass (kg)	54.70	8.92	33.70	79.50
Body weight (kg)	78.82	13.70	45.80	125.00
Height (cm)	167.32	8.04	147.00	187.00
BF%	29.80	7.56	12.50	49.80
WHR	0.95	0.07	0.77	1.16
Physical fitness score	70.04	6.23	53.00	84.00
Obesity degree (%)	132.05	22.02	74.00	194.00
BMI (kg/m ²)	28.06	4.75	15.60	42.30

BMI – body mass index; WHR – waist/hip ratio.

fat percentage (BF%). Fitness scores were determined from the recorded values in reference to ideal body physical condition plotted against ideal values according to age and gender. Based on the ideal body composition and our previous studies, physical fitness scores (PFS) were recorded for each subject. The maximum fitness score calculated is 100, and, based on the prediction equations, we calculated the PFS for each subject. A score of >70 indicted good physical fitness and scores lower than this value indicated poor physical fitness [17].

Statistical Analysis

Data analysis was performed using SPSS (IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.). Descriptive data are expressed as mean± SD along with range (minimum and maximum). Kolmogorov-Smirnov and Shapiro-Wilk tests were performed for normality. Skewed data were analyzed by non-parametric Mann-Whitney test. Normally distributed continuous data groups were compared by the *t* test. Correlation was determined by Spearman's correlation analysis for serum adiponectin, resistin, and A/R ratio with adiposity and insulin resistance indices. We also performed a linear regression analysis with fitness score as the dependent variable and adiponectin, resistin, and A/R ratio as independent variables after adjustment for age and BMI. ROC curve analysis was done to assess the comparative predictive value of physical fitness scores with adiponectin, resistin, and AR ratio. Statistical significance was defined as a *p* value of <0.05.

Results

Table 1 shows the demographic data of all subjects. **Table 2** expresses biochemical and adipokine profile data of all study

participants. **Table 3** shows the correlation of adiponectin, resistin, and AR ratio with adiposity and insulin resistance indices. Adiponectin was correlated positively with PFS ($r=.218$) and negatively with adiposity indices of OD ($r=-.239$), BMI ($r=-.244$), and WHR ($r=-.296$). Additionally, it was correlated negatively with basal insulin ($r=-.211$) and HOMA-IR ($r=-.221$), with *p* for all values <0.05. Resistin was correlated negatively with PFS ($r=-.203$) and positively with WHR ($r=0.176$). AR ratio was correlated positively with PFS ($r=.286$) and negatively with OD ($r=-.210$), BMI ($r=-.222$), WHR ($r=-.308$), and basal insulin ($r=-.237$). Linear regression analysis was performed to assess the relationship of fitness score as the dependent variable with (a) adiponectin, (b) resistin, and (c) AR ratio (**Figure 1**). The relationship was significant for the 3 parameters [adiponectin ($r=.218$, $p=0.015$), resistin ($r=-.203$, $p=0.023$), and AR ratio ($r=.286$, $p=0.001$), respectively]. The participants were dichotomized into 2 groups based on PFS of good and poor scores from our previous research [16,17]. ROC curve analysis was performed to assess the predictive value of fitness scores of adiponectin, resistin, and AR ratio (**Figure 2**). It was observed that individually the value of adiponectin and resistin was nonsignificant, but when AR ratio was taken, the value became significant. Therefore, AR ratio was observed to be a better predictor for PFS, with AUC 64.6% ($p=0.029$).

Discussion

To the best of our knowledge, the present study is the first to determine the correlation of physical fitness assessed by PFS with circulating adipokines adiponectin, resistin, and AR ratio in relation to body adiposity indices. Measures that could increase adiponectin levels and lower resistin levels might be valuable future targets for decreasing the higher coronary artery

Table 2. Lipid profile, insulin indices, and adipokine levels in all study participants.

Analytes	Mean	SD	Minimum	Maximum
FBG (mmol/L)	5.04	0.89	2.90	12.60
Basal Insulin (μ l/ml)	24.20	11.73	14.15	132.15
HOMA-IR	5.50	3.30	2.58	32.30
TC (mmol/L)	4.66	0.90	2.90	6.20
TGs (mmol/L)	1.21	0.72	0.39	6.30
LDL-c (mmol/L)	2.86	0.77	1.61	4.48
HDL-c (mmol/L)	1.17	0.31	0.75	1.57
Serum adiponectin (ng/ml)	120.93	48.86	38.28	308.25
Serum resistin (ng/ml)	2.45	1.08	0.65	5.58
AR ratio	64.67	51.87	15.82	305.63

FBG – fasting blood glucose; HOMA-IR – homeostasis model assessment of insulin resistance; TC – total cholesterol; TGs – triglycerides; LDL-c – low-density lipoprotein cholesterol; HDL-c – high-density lipoprotein cholesterol; AR ratio – adiponectin/resistin ratio.

Table 3. Pearson's Correlation coefficients between adiponectin, resistin, AR ratio, adiposity indices, and insulin resistance index.

	PFS	OD	BMI	WHR	FBG	Basal insulin	HOMA-IR	Adiponectin	Resistin	AR ratio
PFS	1.000									
OD	-.457**	1.000								
BMI	-.424**	.957**	1.000							
WHR	-.561**	.814**	.791**	1.000						
FBG	.093	.000	.035	.071	1.000					
Basal Insulin	-.232**	.339**	.364**	.299**	.121	1.000				
HOMA-IR	-.152	.300**	.332**	.282**	.489**	.906**	1.000			
Adiponectin	.218*	-.239**	-.244**	-.296**	-.122	-.211*	-.221*	1.000		
Resistin	-.203*	.082	.101	.176*	-.215*	.129	.013	-.092	1.000	
AR ratio	.286**	-.210*	-.222*	-.308**	.081	-.237**	-.160	.672**	-.767**	1.000

* $p < 0.05$, ** $p < 0.01$. PFS – physical fitness score; OD – obesity degree; BMI – body mass index; WHR – waist/hip ratio; (FBG – fasting blood glucose; HOMA-IR – homeostasis model assessment of insulin resistance; AR ratio – adiponectin/resistin ratio.

disease (CAD) risk in people with diabetes. This study highlights the importance of exercise and better physical fitness to achieve a better biochemical blood profile that can lower the cardiovascular risk. Moreover, the relative role of the adipokines resistin and adiponectin is reported. Lower levels of adiponectin in obese subjects are inversely related to higher levels of resistin and are considered to be involved in the development of insulin resistance and accelerated atherogenesis [20]. Plasma adiponectin levels are negatively correlated with adiposity. Moreover, low serum adiponectin titers and increased WHR are independently associated with high sensitivity C reactive protein (hsCRP) concentrations in normoglycemic

individuals [21-23]. Since there are gender differences between men and women with regard to adipokine levels, we included only men in the current study to avoid the possibility of the confounding effect of gender [24].

Nayak et al showed that serum adiponectin levels decrease with a rise in adiposity and insulin resistance regardless of diabetes status. Among non-obese subjects, adiponectin was negatively correlated with TG, IL-6, and HOMA-IR and positively correlated with HDL. Diabetes status, tumor necrosis factor- α (TNF- α), and BMI were identified as independent predictors of adiponectin levels. Glucose and adiponectin are useful indicators of

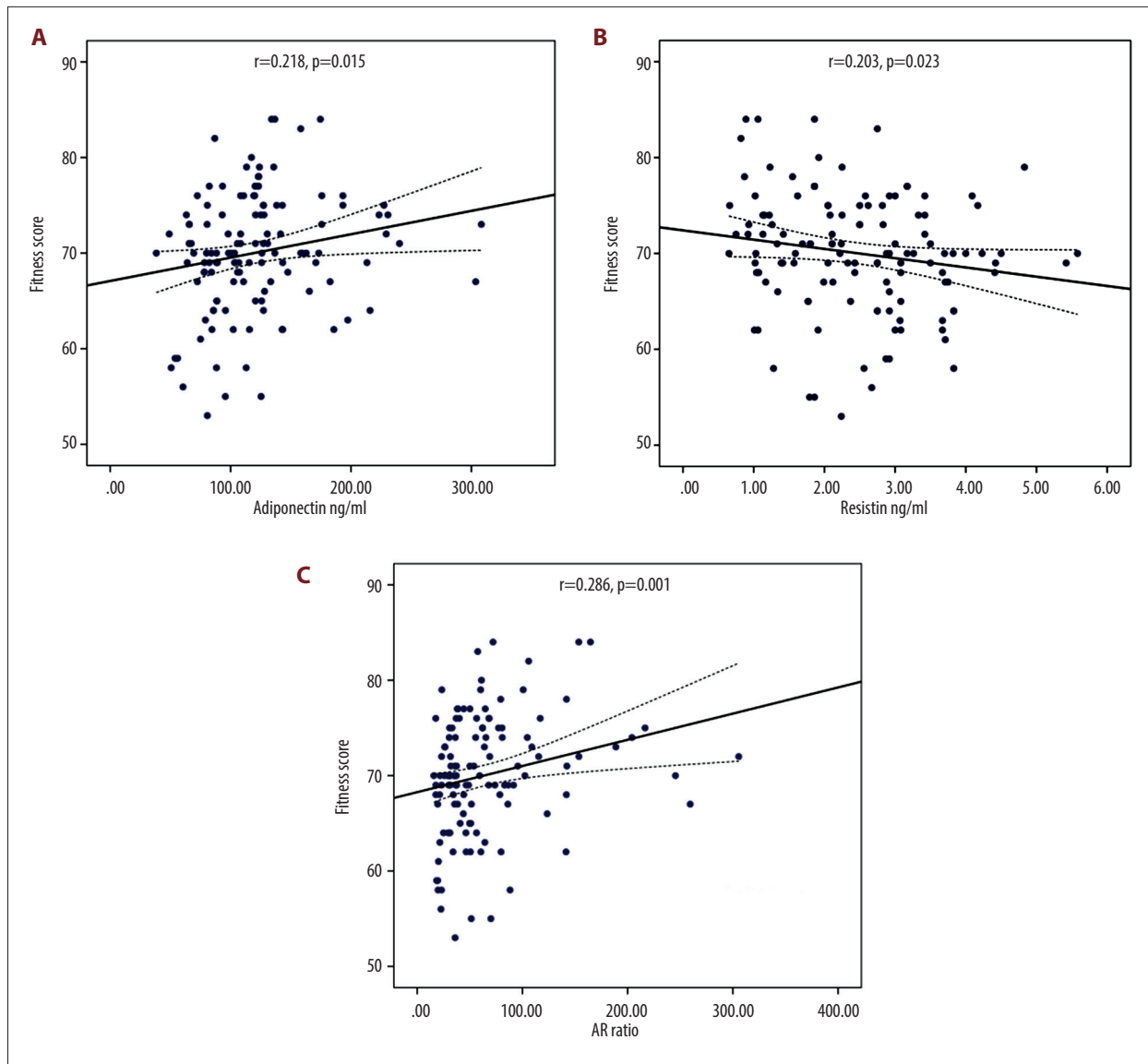


Figure 1. Linear regression analysis of physical fitness scores as dependent variable on (A) adiponectin, (B) resistin, and (C) AR ratio.

T2DM. Moreover, insulin-mediated glucose turnover is significantly affected by adiponectin and $\text{TNF-}\alpha$ [25]. The inverse association of serum adiponectin levels with cardiovascular risk determined by CRP has been reported in African Americans. These results also support our data [26]. Adiponectin was negatively correlated with BMI after adjustment for age, gender, and glycemic state. In an interesting study, Lau et al proposed a novel index of adiponectin and resistin levels combined as an adiponectin/resistin (AR) index and an insulin resistance (IRAR) index. The predictive value of this index was better than adiponectin and resistin levels alone for metabolic dysregulation and disorders. IRAR proved to be a better diagnostic indicator of insulin activity [27].

Different adipocytokines that have been implicated in metabolic syndrome pathogenesis, including leptin, interleukin-6 (IL-6), resistin, $\text{TNF-}\alpha$, angiotensinogen, and plasminogen activator inhibitor-1 (PAI-1) [28]. The present study also reveals that resistin might play an important role in the pathogenic mechanisms leading to high adiposity and insulin resistance. We reported previously that higher resistin levels in T2DM have a significant relationship with body fat mass [29]. Adiponectin is a cardioprotective adipokine; therefore, circulating adiponectin levels are lower in obese individuals [7]. The therapeutic effects of metformin are associated with the upregulation of adiponectin and suppression of leptin and resistin in blood [30].

Possible limitations of the present study are its cross-sectional design, from which a strong causative conclusion cannot

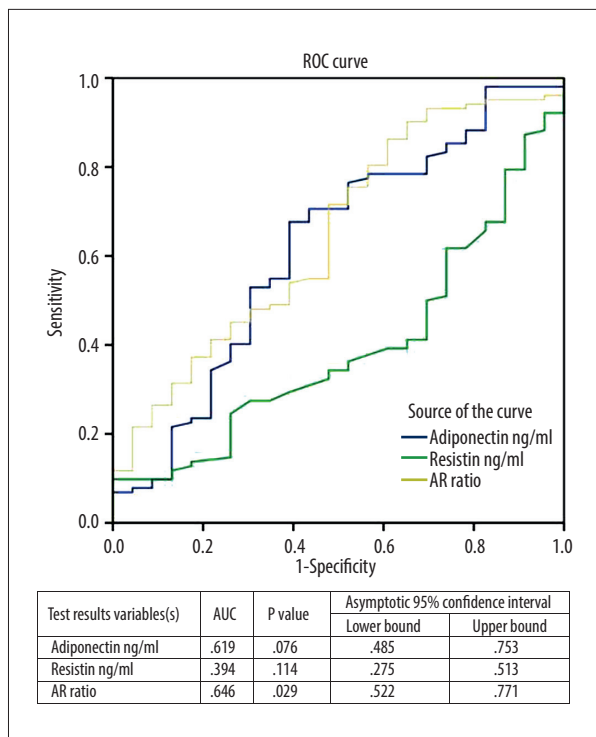


Figure 2. Linear regression analysis of physical fitness scores as dependent variable and its relationship with adiponectin, resistin, and adiponectin/resistin ratio.

be derived. Secondly, we tried to homogenize the group by studying only one gender with lower cardiovascular disease (CVD) risk since they all were normoglycemic. Therefore, we need more studies including females and different ethnicities to explore the contributions of adipokines in obesity and diabetes pathogenesis. Large-scale prospective studies are required to further explore the true homeostatic roles of adiponectin and resistin in relation to obesity and diabetes mellitus. Since these adipokines are related to glucose and lipid metabolism, it would be worth studying them with an integrated approach with prospective studies in relation to different pharmacological interventions, and exercise training programs. This might determine the true role of integrated biomarkers in prediction of metabolic dysfunctions and high cardiovascular risk in obesity.

Conclusions

Serum adiponectin is positively correlated and resistin is negatively correlated with physical fitness scores based on healthy body composition with low proportion of body adiposity and a higher proportion of fat-free mass, which indicates that better fitness has a positive relationship, while increased adiposity has a negative association with adiponectin and resistin. However, the adiponectin/resistin ratio is even more highly associated with physical fitness than adiponectin or resistin alone.

Recommendations

We recommend further research to explore the relationships of adipokines with cardiovascular risk markers, including both traditional and nontraditional risk markers.

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Ethics Approval

The project was approved by College of Medicine IRB committee.

Conflict of Interest

None.

Declaration of Figures Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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