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Full length Research Article

Relationship between Serum Resistin and Insulin Resistance among Obese Non-Diabetic Patients in a Nigerian Tertiary Hospital

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Summary: The prevalence of obesity is soaring globally, particularly in Nigeria, where sedentary lifestyles and dietary changes contribute significantly to its rise. It is linked to various metabolic disorders, including insulin resistance (IR) which is also linked to diabetes mellitus, but the role of resistin, an adipokine, in this context remains contentious. This study aimed to investigate the relationship between serum resistin levels and insulin resistance among non-diabetic obese individuals in Nigeria. This was a hospital-based cross-sectional study involving 200 participants aged 18 to 65 years. Anthropometric measurements, fasting blood glucose, insulin levels, lipid profiles, and serum resistin were assessed. Insulin resistance was calculated using the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR). Statistical analysis was carried out with Mann-Whitney U-test and Spearman's rank correlation coefficient. The obese group exhibited significantly higher BMI, abdominal circumference, waist circumference, hip circumference, waist-hip ratio, fasting blood glucose, insulin levels, and HOMA-IR compared to controls. Lipid profiles and cardiovascular parameters were also significantly elevated in the obese group. However, serum resistin levels did not differ significantly between groups and showed no correlation with BMI or HOMA-IR. In conclusion, circulatory resistin levels were unaffected in non-diabetic obese individuals, suggesting a limited role in insulin resistance among this population. Other adipokines and inflammatory biomarkers may drive insulin resistance in obesity without diabetes. Resistin may not serve as a reliable predictive marker for insulin insensitivity or glucose homeostasis in non-diabetic obesity. Further research is warranted to elucidate the complex interplay of adipokines in metabolic dysfunction among obese individuals.

Keywords*: obesity, resistin, insulin resistance, adiposity, Nigerian, Type 2 diabetes mellitus*

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INTRODUCTION

Globally, the prevalence of obesity has taken an upward trend across all age groups and socioeconomic strata. This trend is not different in Nigeria with the reported rise in the prevalence of obesity, particularly among urban populations and women, a situation attributed partly to sedentary lifestyles and a surge in processed food consumption (Adeloye *et al*., 2021). For instance, the prevalence of overweight and obesity was put at 20.3% and 11.6%, respectively, with around 12 million persons in Nigeria estimated to be obese in 2020. This is indeed worrisome given the socioeconomic burden, psychological impacts, and the heightened morbidity and mortality associated with obesity (Okunogbe *et al*., 2021; Wanjau *et al*., 2023).

Obesity, characterized by excessive accumulation of body fat, places a heavy burden on the metabolic machinery of the body system, thus serving as a potential risk factor for a broad spectrum of debilitating pathophysiological conditions, including insulin resistance (IR), type II diabetes mellitus (T2DM), cardiovascular diseases, and various malignant diseases (Volpe & Gallo, 2023; Yashi & Daley, 2024). The determination and classification of obesity often rely on Body Mass Index (BMI), with the World Health Organization (WHO) defining obesity as a BMI ≥30 kg/m² and overweight as BMI ≥25kg/m² (Woolcott & Seuring, 2022). While BMI serves as a valuable population-scale measure of obesity due to its simplicity and correlation with health risks, other indices such as waist circumference, waist-hip ratio, and body adiposity index provide additional insights into adiposity distribution and associated health risks (Dalton *et al*., 2003).

It is well established that obesity and augmented adiposity contribute to insulin resistance, which in turn cascades into a vicious cycle of glucose intolerance and accumulation of abnormal lipids in the circulation. These interrelated metabolic disturbances significantly increase the risk of developing type 2 diabetes mellitus and

cardiovascular diseases (Kosmas *et al*., 2023; Wondmkun, 2020). The progressive accumulation of fat in adipose cells, independently boosts the synthesis and the release of resistin, one of the range of peptides produced by adipose tissues. This category of molecules, which includes leptin, adiponectin, and other chemokines, have been identified to play pivotal roles in the regulation of appetite, energy expenditure, inflammation, and insulin sensitivity(Clemente-Suárez *et al*., 2023; Yamauchi & Kadowaki, 2013). To this end, a rise of circulatory resistin has been linked with heightened risk of glucose intolerance, dyslipidemia, inflammatory responses, and a variety of unpleasant cardiovascular outcomes (Lehr *et al*., 2012; Park *et al*., 2017).

Specifically, resistin acts by interacting with various proteins involved in inflammatory and metabolic pathways, and interferes with insulin signaling pathways, leading to decreased phosphorylation of insulin receptor substrate 1 (IRS-1) and the inhibition of insulin action in target tissues, consequently, contributing to insulin resistance in various tissues. As such, suppressed adiponectin levels and reciprocal elevation of circulatory resistin levels have been proposed as predictive markers for future diabetes risk in obese individuals (Su *et al*., 2019).

Furthermore, insulin resistance, characterized by decreased responsiveness of target tissues to insulin, is a central feature of obesity-related metabolic disturbances. The Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), a measure derived from fasting glucose and insulin levels, serves as a marker for evaluating insulin resistance and impaired insulin sensitivity in excess adiposity (Matthews *et al*., 1985). Therefore, in obese individuals, the dysregulation of glucose and lipid metabolism leads to elevated HOMA-IR scores, which could be interpreted as impaired insulin signaling pathways and glucose homeostasis. Furthermore, studies suggest that resistin levels are positively correlated with HOMA-IR values, indicating a potential role in exacerbating insulin resistance (Steppan *et al*., 2001).

As it stands, the relationship between resistin, IR, and lipid profile in humans is enveloped in equivocation, with some studies suggesting positive correlations between resistin with IR and lipid profile in obese individuals (Pandey, 2018), while other investigations suggest otherwise (Amirhakimi *et al*., 2011). Also, there is paucity of information on the possible role of resistin in the obese non-diabetic in our environment. Although the prevalence of obesity is on the upward trend in Nigeria accompanied by a range of metabolic disorders like insulin resistance and type 2 diabetes mellitus (T2DM), the specific factors contributing to insulin resistance in obese individuals are not well understood in the study population. Investigating the relationship between resistin and insulin resistance in obese Nigerian patients is crucial to the understanding of the underlying mechanisms of metabolic dysfunction in this population. Therefore, this current study attempts to investigate the relationship between serum resistin and insulin resistance among non-diabetic obese patients.

MATERIALS AND METHODS

Ethical Consideration: Approval was obtained from the Health Research and Ethical Committee of the Lagos University Teaching Hospital with protocol number ADM/DCST/HREC/APP/2775 on 3rd April 2019, and was conducted in compliance with the Declaration of Helsinki (Ehni & Wiesing, 2024). Prior to inclusion in the study and data collection, informed and written consent was obtained from all participants. Each recruited participant was assigned numerical codes, and their clinical data and test results were securely stored to maintain confidentiality during the study.

Study Design and Setting: This was a cross-sectional study conducted at Lagos University Teaching Hospital (LUTH), Lagos State, Nigeria, a tertiary hospital which serves as a referral center with approximately 800-bed spaces. The study was conducted between May 2019 and May 2020 (a period of 12 months).

Participants in this study included male and female subjects aged 18 to 65 years attending the LUTH General Outpatient Clinic and the Obesity and Metabolic Clinic of the Department of Clinical Pathology who were recruited using a simple random sampling method based on the order of registration. The minimum sample size was determined to be 97 using the formular ($n = [Z2.P.(1 – p)] \div E2$) (Daniel & Cross, 2019) where N is the sample size, Z is the standard deviation (1.96), p is the prevalence of obesity in Nigeria (6.8%)(Chigbu, 2018), and d is the level of significance (0.05). A sample size of 200 (100 each for the obese and control groups) was used.

The study included apparently healthy men and women aged 18 to 65 years with a BMI equal to or greater than 30 kg/m², classified as obese participants, while control participants comprised apparently healthy individuals with a BMI ranging from 18.5 kg/m² to 24.9 kg/m². Exclusion criteria included diabetic individuals, cancer patients, smokers, and pregnant women due to the potential confounding factors impacting resistin levels and BMI calculations.

Data Collection: Patient demographic and clinical data was obtained by the use of a structured interviewer-administered questionnaires. Anthropometric measurements like weight was measured using a weighing scale, height using a stadiometer, and BMI was calculated from the weight and height measurements.

Waist circumference was measured using a stretch-resistant tape, wrapped around the subjects at a level parallel to the floor, midpoint between the top of the iliac crest and the lower margin of the last palpable rib in the mid auxiliary line while the hip circumference was at a level parallel to the floor, at the largest circumference of the greater trochanter. Both measurements were taken three times for each participant. Abdominal obesity was defined using the recommended criteria of waist circumference >88 cm in women and greater than 102cm in men while Waist-hip ratio was computed by dividing the waist circumference by the hip circumference, both in centimeter.

Measurement of cardiovascular parameters: Following a 5 minute of rest in sitting position, systolic and diastolic blood pressure (SBP and DBP) were recorded three times within 1-2 minutes interval with automated sphygmomanometer (Omron), which has been standardized with mercury sphygmomanometer prior to the study. The

mean of the two closest readings for SBP, DBP and pulse rates are then recorded for the participants. The mean arterial pressure (MAP) was subsequently calculated as follows: DBP + 1/3(SBP - DBP), while myocardial oxygen demand (MOD) was derived as the product of pulse rate and SBP.

Sample Collection and Assays: Ten milliliters of venous blood were collected from each participant and stored at -20°C for up to three months before analysis. Glucose levels were measured using a quantitative-enzymatic-spectrophotometric method involving the glucose oxidase (GOD) method. Insulin levels were determined using a Calibiotech ELISA kit, which involves a solid-phase enzyme immunoassay with monoclonal antibodies against insulin, measured at 450 nm. Insulin resistance was calculated using the HOMA-IR formula: (glucose × insulin)/22.5.

Serum lipids, including total cholesterol, triglycerides, and HDL-cholesterol, were also measured using quantitative-enzymatic-spectrophotometric methods, with absorbance measured at 500 nm. Remnant cholesterol was calculated from a standard lipid profile as total cholesterol minus the LDL cholesterol and HDL cholesterol (Nordestgaard & Varbo, 2014). Serum resistin levels were analyzed using a Human RETN ELISA kit, employing a sandwich-ELISA method with pre-coated microplate wells containing antibodies specific to human resistin, and absorbance was measured at 450 nm.

Statistical Analysis: Data were presented as medians and interquartile ranges (IQR) to describe the distribution of variables in the two groups of participants. The Mann-Whitney U test, also known as the Mann-Whitney-Wilcoxon test, was used to compare differences between the medians of the two groups with non-parametric data distribution and it was conducted with a confidence interval of 95%. Statistical analysis was performed using SPSS GraphPad 5 software package (USA). Additionally, correlations between serum resistin levels and various clinical parameters were analyzed using Spearman's rank correlation coefficient. All statistical tests were two-tailed, and p-values less than 0.05 were considered statistically significant.

RESULTS

There were no significant differences in mean age, gender distribution, education level, or religion between the obese and control groups. However, a marginally significant difference was observed in marital status, with a higher percentage of the obese group being married compared to the control group (n=81 versus n=69; $\chi^2 = 3.840$, p = 0.050) (Table 1). Significant differences were found in several anthropometric and glycemic parameters between the obese and control groups.

Table 1:
Sociodemographic characteristics of the study population (n= 200)

Variable		Obese (N=100)	Control (N=100)	X^2	p-value
Age *(year; mean* ±SD*)*		4 1.5± 11.7	40.5 ± 12.8	-0.600	0.549
Gender	Male	39 (39.0%)	45 (45.0%)	0.739	0.390
	Female	61 (61.0%)	55 (55.0%)		
Marital status	Single	19 (19.0%)	31 (31.0%)	3.840	0.050
	Married	81 (81.0%)	69 (69.0%)		
Education	None	1 (1.0%)	3 (3.0%)	4.532	0.209
	Primary	4 (4.0%)	6 (6.0%)		
	Secondary	29 (29.0%)	39 (39.0%)		
	Tertiary	66 (66.0%)	52 (52.0%)		
Religion	Christian	85 (85.0%)	87 (87.0%)	0.166	0.684
	Muslim	15 (15.0%)	13 (13.0%)		

independent t-test statistic,Chi-square statistic,*
[a]Fisher's exact test, adjusting for cells containing values less than 5

The obese group had significantly higher median BMI (33.4 kg/m² versus 25.3 kg/m², p < 0.0001), abdominal circumference (104.0 cm versus 86.0 cm, p < 0.0001), hip circumference (112.0 cm versus 98.0 cm, p < 0.0001), waist circumference (100.0 cm versus 84.0 cm, p < 0.0001), and waist-hip ratio (0.88 versus 0.84, p = 0.0002). Additionally, median fasting blood glucose (5.20 mmol/L versus 4.60 mmol/L, p = 0.0001), insulin levels (13.0 µU/mL versus 4.81 µU/mL, p < 0.0001), and HOMA-IR (3.02 versus 0.93, p < 0.0001) were significantly higher in the obese group. Notably, there was no significant difference in serum resistin levels in both groups of participants (Table 2).

In terms of lipid profiles and cardiovascular parameters, the obese group had significantly higher median triglyceride levels (1.00 mmol/L versus. 0.88 mmol/L, p = 0.0004), total cholesterol (4.34 mmol/L versus. 4.21 mmol/L, p = 0.017), LDL cholesterol (2.73 mmol/L versus. 2.54 mmol/L, p = 0.009), and remnant cholesterol (0.45 mmol/L versus. 0.40 mmol/L, p = 0.002).

Table 2:
Arthrometric and Glycemic parameter in non-obese and obese Nigerians

Parameters	Non-obese median	IQR	Obese median	IQR	P value
BMI (kg/m2)	25.3	23.3-27.1	33.4	33.34 -36.31	<0.0001
Abdominal circumference	86.0	81.0-94.0	104.0	96-112.5	<0.0001
Hip circumference	98.0	93.0-104.0	112.0	108-119.0	<0.0001
Waist circumference	84.0	79.0-91.0	100.0	93.0-107.0	<0.0001
Waist-hip ratio	0.84	0.81-0.90	0.88	0.84-0. 0.94	0.0002
FBG (mg/dl)	4.60	4.2-5.2	5.20	4.55-5.90	0.0001
Insulin (mIU/ml)	4.81	3.30-6.77	13.0	9.44-19.31	<0.0001
HOMA-IR	0.93	0.67-1.41	3.02	2.16-4.71	<0.0001
Resistin	1.63.	1.45-1.74	1.63	1.52-1.70	0.586

*Data presented as median, and the distribution between the non-obese and obese compared with Mann -Whitney test; *p<0.05 vs non-obese is significantly higher. MOD: myocardial oxygen demand of oxygen*

Conversely, HDL cholesterol was significantly lower in the obese group (1.07 mmol/L versus. 1.23 mmol/L, p = 0.0003). The obese group also had significantly higher median systolic blood pressure (132.0 mmHg versus. 125.0 mmHg, p = 0.033), diastolic blood pressure (86.0 mmHg versus. 81.0 mmHg, p = 0.033), mean arterial pressure (96.0 mmHg versus. 88.0 mmHg, p = 0.033), and myocardial oxygen demand (10578.0 versus. 9690.0, p = 0.015) (Table 3).

Regarding serum resistin levels, there were no statistically significant differences across BMI categories or HOMA-IR levels. There was no significant correlation between serum resistin levels and BMI (r = 1.780, p = 0.152). as well as serum resistin level and HOMA-IR (r = -0.613, p = 0.540) (Table 4).

Table 3:
Relationship between serum resistin, body mass index and HOMA-IR among the study participants

Variable	n	Serum resistin (Mean±SD)	Spearman's correlation	p value
BMI				
Normal	100	1560.53±285.04	1.780	0.152
Obese class I	66	1465.66±436.04		
Obese class II	23	1591.81±200.17		
Obese class III	11	1641.67±55.72		
HOMA-IR				
<2	110	1524.25±345.92	-0.613	0.540
≥2	90	1553.22±314.64		

Table 4:
Lipid Profiles and Cardiovascular parameter in non-obese and obese participants

Parameters	Non-obese(n=100)	IQR	Obese (n=100)	IQR	p value
Triglycerides (mmol/L)	0.88	0.68-1.12	1.00*	0.85-1.42	0.0004
Total Cholesterol(mmol/L)	4.21	3.62-4.73	4.34*	3.79-5.28	0.017
HDL Cholesterol(mmol/L)	1.23	1.03-1.42	1.07*	0.89-1.24	0.0003
LDLCholesterol(mmol/L)	2.54	1.97-2.95	2.73*	2.24-3.57	0.009
Remnant Cholesterol	0.40	0.31-0.51	0.45*	0.85-1.42	0.002
SBP (mmHg)	125.0	118.0-142.0	132.0*	121.5-144.5	0.033
DBP (mmHg)	81.0	75.0-91.0	86.0*	80.0-92.0	0.033
MAP (mmHg)	81.0	75-91	86.0*	80.0-92.0	0.033
MOD	9690.0	8160-11543	10578*	9348.0-12077	0.015

Data presented as median, and the distribution between the no-obese and obese compare with Mann -Whitney test ; *p<0.05 versus non-obese is significantly higher. MOD: myocardial oxygen demand of oxygen

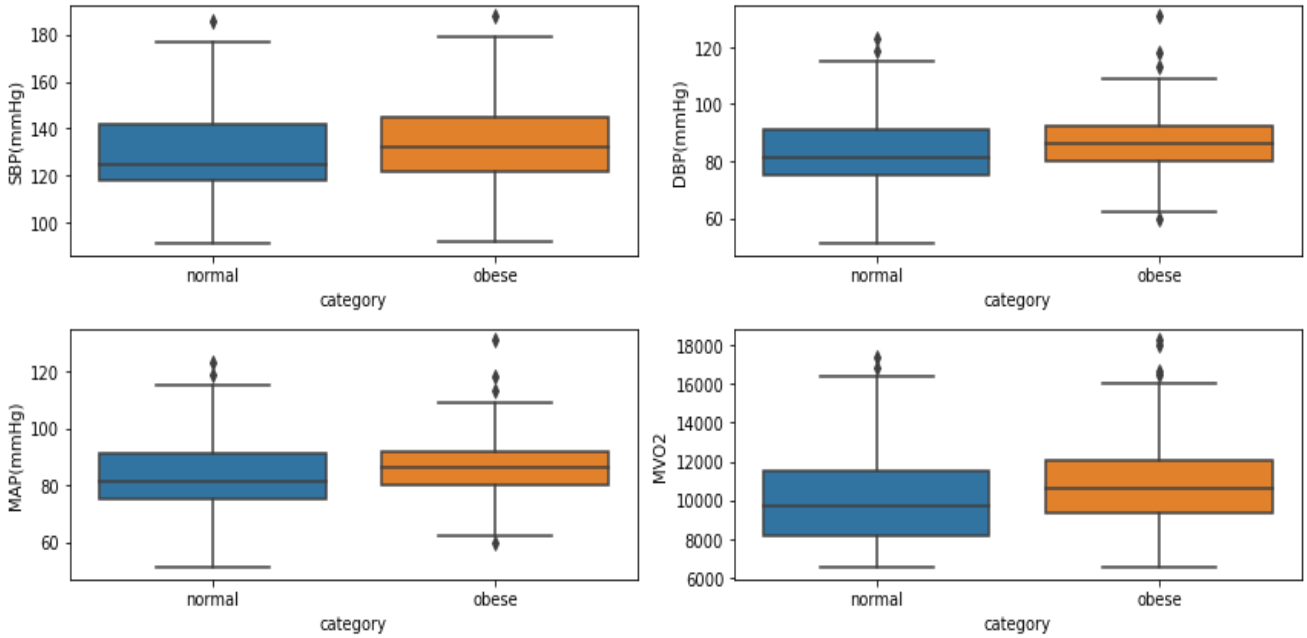

Figure 1:
Distribution of FBG, serum insulin ,HOMA-IR I and Resistin in obese and non-obese participants, with the obese showing significantly higher median value with the exception of resistin ,*p<0.05, Manny-Whitney test

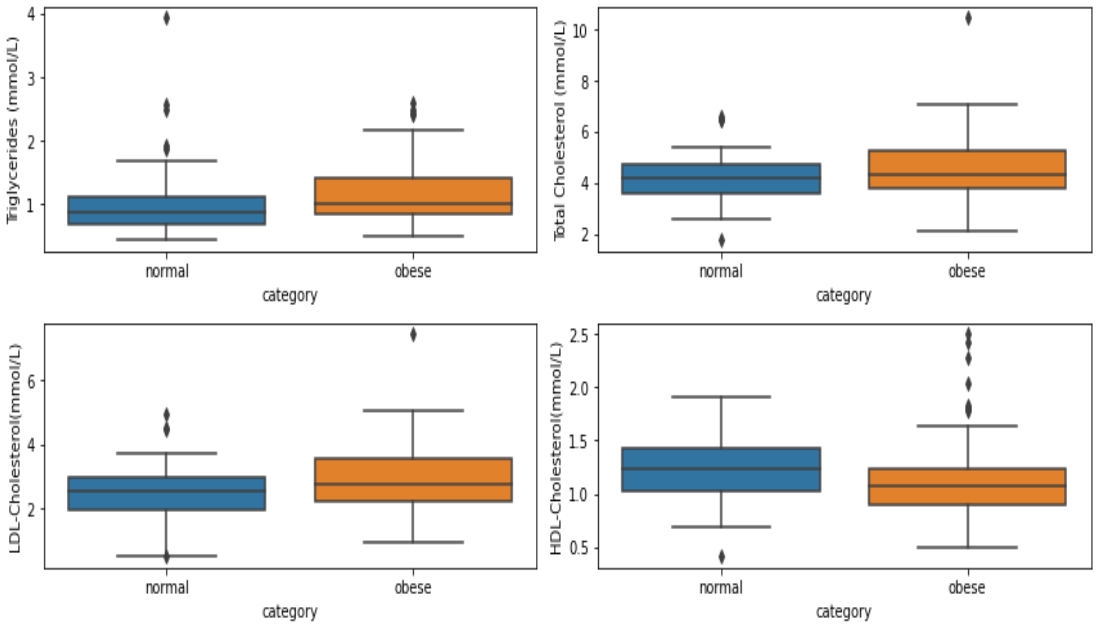

Figure 2:
Distribution of SBP, DBP, MAP and MOD in obese and non-obese participants, with the obese showing significantly higher median value,*p<0.05, Manny-Whitney test.

DISCUSSION

The obese group in our current study demonstrates clear evidence supporting the presence of insulin resistance otherwise referred to as insulin insensitivity, as reflected by higher HOMA-IR and corresponding elevated fasting serum insulin level in them compared to the records in the non-obese group. The higher HOMA-IR indicates that insulin resistance was significantly higher in the obese condition compared to the non-obese condition, an observation that is in line with previous study reporting an unprecedented high prevalence of insulin resistance in young non-diabetic obese persons (Elrayess *et al*., 2020). This is indeed instructive, as our finding invariably suggests that the obese participants in our study are currently prediabetic and could be on their ways to full-blown diabetic condition.

Enhanced tissue adiposity, characterized by excessive fat in visceral tissue, is a fundamental hallmark in obesity with the potential to drive insulin resistance (Hocking *et al*., 2013). In particular, hyperinsulinemia typically results from attenuated peripheral responses of adipose tissue and muscle cells to insulin signal (Saltiel & Kahn, 2001). Without equivocation, the participants with obesity clearly presented with evidence of augmented adiposity as supported by their higher abdominal circumference, waist circumference, hip circumference, waist-hip-ratio, and BMI characteristic of increased adiposity (Després & Lemieux, 2006; Jeong *et al*., 2023; Ross *et al*., 2020).

Aside from serving as a potential breeding ground for insulin resistance, exaggerated tissue adiposity especially in visceral cells is also a trigger for dyslipidemia (Fabbrini *et al*., 2009; Vega *et al*., 2006), a metabolic condition characterized by accelerated release of fatty acids from adipose tissue, suppressed clearance of blood cholesterol resulting from reduced HDL and reciprocal elevated LDL. The picture above of lipid dysregulation with overall accentuation of total blood cholesterol, LDL cholesterol, remnant cholesterol and triglyceride in the obese group in our study aligns with previous study (Finn *et al*., 2010; Vekic *et al*., 2019). It is also imperative to state that insulin resistance influences the accumulation of bad fat in blood as observed in this current study, and the plausible mechanisms advanced for this is the disruption of lipid metabolism via the potentiation of hepatic fat release, blunted lipoprotein lipase activity, and increased LDL cholesterol at the expense of HDL cholesterol (Chung *et al*., 2022; Liu & Li, 2015). Overall, the dyslipidemia engendered by insulin resistance and augmented adiposity is an important cardiovascular risk factor implicated in arterial pathological condition like coronary heart disease. In particular, high concentrations of remnant cholesterol as seen in the obese group in our study, has been identified as a potential residual risk of cardiovascular disease even when LDL cholesterol is lowered (Langsted *et al*., 2020).

It is therefore not surprising to observed a higher level of systolic, diastolic and mean arterial blood pressure with corresponding rise in myocardial oxygen demand in the obese group in our study. Most importantly, the combined elevation of remnant cholesterol and myocardial oxygen demand in the obese group further accentuates the risk of coronary heart disease among this group. The central role played by insulin resistance in driving blood pressure involved interconnected mechanisms which increases sympathetic nervous system activity (Russo *et al*., 2021), endothelial dysfunction (Muniyappa *et al*., 2020), renal sodium retention (Brosolo *et al*., 2022), renin-angiotensin-aldosterone system activation, proinflammatory oxidative stress (Sarafidis & Ruilope, 2006), disruptions in vascular growth and remodeling (Muniyappa *et al*., 2007). Furthermore, while obesity results in adiposity dysfunction, insulin resistance is also known to promote adipose tissue dysfunctions. Therefore, it is held that insulin resistance and adipose tissue dysfunction works in vicious cycle, with each condition exacerbating the other to worsen the progression of metabolic syndrome in obese patients.

Furthermore, adipose tissue performs pertinent metabolic regulatory functions through the actions of different molecules referred to as adipokines that could be potentially exaggerated in obesity, insulin resistance and other metabolic conditions. These molecular peptides

include resistin, adiponectin, leptin, chemerin, visfatin, and vaspin, adipokines alongside other inflammatory cytokines and chemokines. Surprisingly, resistin was unaltered in the obese group when compared with the non-obese group, a finding that is at variance with a previous study that reported significantly higher level of circulatory resistin among obese non-diabetic Nigerians (Onyemelukwe *et al*., 2022), same with the result obtained in a study conducted among Saudi Arabian women (Al-Harithy & Al-Ghamdi, 2005).

Most importantly, some studies have indicated that resistin levels are often elevated in conditions related to insulin resistance, including condition like obesity and type 2 diabetes (Reilly *et al*., 2005; Yang *et al*., 2005). Therefore, contrary to our expectation resistin level was apparently unaffected in our non-diabetes obese group. Although the reason for this is somewhat elusive, some works have nonetheless provided empirical evidence that exaggerated insulin level possesses the potential to modulate and suppress resistin level (Lee *et al*., 2003). Perhaps, insulin resistance self-regulated the level of resistin it produces in some subsets of obese individuals who have not developed full-fledged type 2 diabetes mellitus. It is therefore safe to infer that the insulin resistance in our obese groups could have likely attenuated the anticipated exaggerated resistin response to insulin resistance among the investigated obese participants.

In conclusion, obesity did not significantly alter circulatory resistin among a cross-section of non-diabetic obese individuals in this study, rather the level was comparable to the non-obese group. Also, no association was found between circulatory resistin and insulin resistance. Other adiposity indices like BMI, waist-hip ratio and abdominal circumference were not also significantly correlated with circulatory resistin in the obese non-diabetic state. This invariably supports the preponderant of interplay of other adipokines and inflammatory biomarkers as the likely engine behind the observed insulin resistance in obesity with no associated diabetes mellitus. The apparent silence of circulatory resistin in obesity may explain the moderation in the non-diabetic fasting glucose level amidst this condition although noticeably high. Most likely resistin may not be the primary driver of insulin resistance until a threshold cut off is attained and exceeded. As such, circulatory resistin may not offer a high predictive value for insulin insensitivity and glucose homeostasis in the obese non-diabetic individual.

List of Abbreviations

BMI: Body Mass Index; IR: Insulin Resistance; T2DM: Type 2 Diabetes Mellitus; WHO: World Health Organization; HOMA-IR: Homeostatic Model Assessment of Insulin Resistance; LUTH: Lagos University Teaching Hospital; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; MAP: Mean Arterial Pressure; MOD: Myocardial Oxygen Demand; LDL: Low-Density Lipoprotein; HDL: High-Density Lipoprotein; IQR: Interquartile Range

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