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Association of Adipokines, Oxidative Stress Markers, and Metabolic Enzymes in Obesity-Associated Insulin Resistance

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Abstract: Background: Obesity-associated insulin resistance involves adipokine dysregulation, oxidative stress, and altered metabolic enzyme activity, contributing to impaired glucose homeostasis and metabolic dysfunction. Aims of the study: To evaluate associations between adipokines, oxidative stress markers, metabolic enzymes, and insulin resistance among individuals with obesity. Methodology: An analytical case-control study included 150 adults aged 18–55 years: 100 patients with obesity-associated insulin resistance (BMI ≥ 30 kg/m²; HOMA-IR ≥ 2.5) and 50 normal-weight healthy controls. Fasting blood samples were analyzed for glucose, lipid profile, liver enzymes, LDH, insulin, adipokines, MDA, SOD, and GPx using standard biochemical, ELISA, and spectrophotometric methods. HOMA-IR was calculated from fasting glucose and insulin concentrations. Result: Participants with obesity-associated insulin resistance showed significantly higher BMI, waist circumference, blood pressure, glucose, insulin, HOMA-IR, and atherogenic lipids. Leptin, resistin, MDA, ALT, AST, and GGT were elevated, whereas adiponectin, SOD, GPx, and HDL-C were reduced. HOMA-IR correlated positively with leptin, resistin, MDA, ALT, and GGT and negatively with adiponectin, SOD, and GPx. Multivariable analysis identified BMI, leptin, MDA, GGT, adiponectin, and SOD as independent correlates of HOMA-IR. Conclusions: Obesity-associated insulin resistance was characterized by adipokine dysregulation, increased oxidative stress, and metabolic disturbances. BMI, leptin, MDA, GGT, adiponectin, and SOD were independently associated with HOMA-IR, supporting their potential relevance as metabolic indicators.

Keywords: Adipokines; Insulin resistance; Obesity; Oxidative stress; Metabolic enzymes.

1. Introduction

Obesity is a long-term, complex metabolic disease due to abnormal and/or excessive amount of adipose tissue accumulation and associated with a risk of developing type 2 diabetes mellitus, metabolic dysfunction-associated steatotic liver disease, cardiovascular diseases and other chronic diseases [1]. BMI is commonly used as a cut-off for obesity but people can be similarly obese but have very different metabolic patterns. This heterogeneity suggests that obesity's metabolic effects depend not only on the amount of fat tissue, but also on the distribution of the visceral fat, the function of fat cells, the presence of fat in the wrong place, inflammation and insulin sensitivity [2]. A central mechanism linking obesity to cardiometabolic complications is insulin resistance, defined

as the failure of these key tissues, namely skeletal muscle, liver and adipose tissue, to respond appropriately to the effects of insulin in the ways that they should [3].

Adipose tissue is an active endocrine gland that produces biologically active mediators called adipokines. These molecules control appetite, energy expenditure, glucose and lipid metabolism, vascular function, inflammation and insulin signalling [4]. Obesity, through adipocyte hypertrophy, induces extracellular-matrix remodeling, macrophage infiltration, hypoxia and changes in adipokine secretion in the adipose tissue. This abnormal pattern is often associated with elevated plasma levels of pro-inflammatory adipokines and leptin, and a decrease in adiponectin production [5]. This imbalance leads to chronic low-grade inflammation and to impairments in insulin-receptor signaling through c-Jun N-terminal kinase, nuclear factor- κ B and inhibitory serine phosphorylation of insulin-receptor substrates [6].

The insulin-sensitizing, anti-inflammatory, and fatty-acid-oxidizing effects of adiponectin involve its receptors, as well as the activation of AMP-activated protein kinase and peroxisome proliferator-activated receptor- α . The decreased adiponectin levels seen in obesity can then lead to increased glucose production from the liver, fat deposition and insulin resistance in the periphery [7]. On the other hand, leptin levels tend to rise in line with adipose mass. However, many obese persons have elevated levels of leptin in the blood and become resistant to the effects of the hormone, which can reduce the ability to inhibit appetite and may increase inflammatory and metabolic dysfunction. Other adipocyte/macrophage-derived mediators such as resistin could continue to affect glucose homeostasis and increase inflammatory signaling [8]. Therefore, the adiponectin/leptin ratio could be a better indicator of adiposetissue dysfunction and insulin resistance than either adiponectin or leptin alone [9].

Another factor of obesity-related insulin resistance is oxidative stress. High nutrient availability, mitochondrial overload, activation of NADPH-oxidase, endoplasmic-reticulum stress and adipose inflammation lead to increased production of reactive oxygen and nitrogen species [10]. If the production of oxidants is greater than the capacity of the antioxidants to neutralize them, cellular proteins, membrane lipids and nucleic acids can be damaged by oxidants. Reactive species may also affect insulin signaling, affect glucose-transporter translocation, alter mitochondrial function and promote pancreatic β -cell dysfunction [11]. The measurement of malondialdehyde is used as an indicator of lipid peroxidation, while glutathione, superoxide dismutase, catalase, glutathione peroxidase and total antioxidant capacity are used to measure other parts of antioxidant defense [12]. The antioxidant responses can, however, differ depending on the duration of obesity, metabolic phenotype, diet, age, and the severity of the disease, so that multiple markers would be better than just one oxidative parameter to evaluate [13]. The relationships among oxidative status, body composition, glucose metabolism and insulin resistance have been shown to be significant in obese individuals, but not all populations share these relationships [14].

Metabolic enzymes could offer another biochemistry of insulin resistance in obesity. Alanine aminotransferase, aspartate aminotransferase and γ -glutamyl transferase may all reflect hepatic metabolic stress, ectopic fat accumulation, oxidative injury, or subclinical hepatocellular dysfunction. They have been linked to adiposity and insulin resistance despite being within the usual laboratory reference ranges [15]. Hepatic and systemic insulin resistance are biologically connected, as obesity and insulin resistance can act together to enhance the chance of abnormal liver-enzyme activity [16]. However, aminotransferases are not specific indicators of insulin resistance, and if their levels are abnormal, the influence of hepatic disease, drug therapy, alcohol consumption, and other factors must be taken into account [17]. Diet-induced weight loss has also resulted in a substantial improvement in oxidative and metabolic biomarkers that has occurred along

with improvements in adiposity and insulin sensitivity, suggesting that these pathways are not static, but instead are dynamic [18].

Although there are known biological links between the domains of adipose-tissue dysfunction, oxidative stress, hepatic metabolism and impaired insulin action, these are typically assessed separately. Together, their combined assessment may offer a more integrated picture of metabolic deterioration in obesity, and it might be possible to differentiate metabolically healthy obesity from excess adiposity, which has low insulin resistance.

The objectives of the present study were to assess the levels of circulating adipokines, oxidative stress markers, selected metabolic enzymes in individuals with obesity related insulin resistance, to explore their relationships with anthropometric and glycemic indices and to identify those independent biomarker parameters that were associated with insulin resistance.

2. Methodology

This analytical case-control study was conducted at Nasiriyah General Hospital, Thi-Qar Governorate, Iraq, to explore the correlation of adipokines, oxidative stress markers and some metabolic enzymes with insulin resistance associated with obesity from September 1, 2025 to June 30, 2026. Fifteen hundred adults (18-55 years old) were enrolled and separated into 100 patients with obesity-related insulin resistance and 50 normal weight controls who appeared healthy. Patients were eligible for study if they met the following criteria: insulin resistance based on homeostatic model assessment of insulin resistance (HOMA-IR) ≥ 2.5 , which was calculated as fasting insulin ($\mu\text{IU/mL}$) $\times$ fasting glucose (mg/dL)/405, and a body mass index (BMI) $\geq 30 \text{ kg/m}^2$. Control participants were within BMI range $18.5\text{--}24.9 \text{ kg/m}^2$ with normal fasting glucose levels, no clinical signs of insulin resistance and a HOMA-IR < 2.5 . The exclusion criteria were: previously diagnosed diabetes mellitus, endocrine disorders, affecting body weight or glucose metabolism, chronic liver or kidney disease, cardiovascular disease, active inflammatory or infectious disorders, autoimmune diseases, malignancy, pregnancy or lactation, and current use of corticosteroids, insulin-sensitizing agents, lipid-lowering medications, antioxidant supplements, and drugs known to affect glucose metabolism. The data collection was done using a standardized data collection form, which included demographic data (age, sex, residence, smoking status, family history of type 2 diabetes) along with clinical parameters (blood pressure, weight, height, BMI and waist circumference). Venous blood was obtained from all individuals after 8-12 hours of fasting; about 10 mL of venous blood was collected in a fluoride tube for determination of fasting glucose, while the remaining venous blood was collected in serum-separator tube and allowed to clot for about 20-30 minutes before centrifugation at 3000 rpm for 10 minutes. Blood serum was separated immediately and aliquots were stored at -80°C without repeated freeze-thawing until analyzed for biomarkers. The fasting glucose, total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, ALT, AST, GGT and LDH were determined by using the standard enzymatic colourimetric method in an automated clinical chemistry analyzer. Serum fasting insulin, leptin, adiponectin and resistin levels were measured by commercially available enzyme-linked immunosorbent assay (ELISA) kits following the manufacturers' instructions. Serum malondialdehyde (MDA) level was measured by the thiobarbituric acid-reactive substances (TBARS) method and the activities of superoxide dismutase (SOD) and glutathione peroxidase (GPx) were measured by spectrophotometric assay kits. Insulin resistance was measured by HOMA-IR and all laboratory values were run in duplicate if applicable and using internal controls with each analytical run.

Statistical analysis

IBM SPSS Statistics version 26.0 was used for statistical analyses. Normal distribution of continuous variables was tested using the Shapiro-Wilk test, and they were presented

as mean $\pm$ SD for normally distributed variables and median (IQR) for non-normally distributed variables, while categorical variables were presented as frequency and percentage. The independent-samples t-test or the Mann–Whitney U test was used for between-group comparisons for continuous variables, and the chi-square test or Fisher's exact test was used for categorical variables. Spearman's rank correlation was used to determine associations between HOMA-IR and adipokines, oxidative stress markers and metabolic enzymes. Then, multivariable linear regression analysis was done to identify factors independently associated with HOMA-IR after adjusting for relevant confounders: age, sex, BMI; and fasting glucose and insulin were not used as independent variables because they were mathematical parts of HOMA-IR equation. Before entering variables into the final model, multicollinearity was checked and variables were included if a two-tailed P value <0.05 was obtained.

Ethical approval

This study protocol has been reviewed and approved by the appropriate research ethics committee of the institution involved and was carried out in compliance with the Declaration of Helsinki. All participants gave written informed consent prior to participation and personal and laboratory data were kept confidential throughout the study.

3. Results

Comparison of sociodemographic, anthropometric, familial, and blood-pressure characteristics between the two study groups

The age, sex, urban living, and current smoking status did not differ between the groups (all $P>0.05$), as shown in Table 1. Insulin-resistant participants had a higher proportion with a family history of type 2 diabetes than controls (43.0% vs. 24.0%, $P=0.023$). BMI, waist circumference, systolic BP and diastolic BP (all $P \leq 0.001$) were significantly higher in the insulin resistant group.

Table 1. Baseline Characteristics of Participants with Obesity-Associated Insulin Resistance and Healthy Controls

Variable	Obesity with insulin resistance (n=100)	Healthy controls (n=50)	P value
Age, years	36.9 $\pm$ 9.8	35.7 $\pm$ 9.4	0.475
Male sex, n (%)	58 (58.0)	27 (54.0)	0.642
Female sex, n (%)	42 (42.0)	23 (46.0)	
Urban residence, n (%)	67 (67.0)	36 (72.0)	0.535
Current smoking, n (%)	21 (21.0)	8 (16.0)	0.466
Family history of type 2 diabetes, n (%)	43 (43.0)	12 (24.0)	0.023
BMI, kg/m ²	34.7 $\pm$ 3.8	23.6 $\pm$ 2.2	<0.001
Waist circumference, cm	107.4 $\pm$ 10.2	82.3 $\pm$ 8.7	<0.001
Systolic BP, mmHg	128.6 $\pm$ 12.7	119.8 $\pm$ 10.9	<0.001
Diastolic BP, mmHg	81.9 $\pm$ 8.4	77.2 $\pm$ 7.5	0.001

Comparative assessment of glucose homeostasis, insulin resistance, and circulating lipid parameters between the study groups

As presented in Table 2, fasting glucose, fasting insulin, HOMA-IR, total cholesterol, triglycerides, and LDL-C were found to be significantly higher in participants with obesity-associated insulin resistance when compared to healthy controls. HDL-C levels were significantly lower in the insulin-resistant group, in contrast. All intergroup differences were statistically significant ($P \leq 0.001$), suggesting poor glucose regulation and atherogenic lipid profile.

Table 2. Glycemic and Lipid Profiles of Participants with Obesity-Associated Insulin Resistance and Healthy Controls

Parameter	Obesity with insulin resistance (n=100)	Healthy controls (n=50)	P value
Fasting blood glucose, mg/dL	108.6 ± 13.9	88.9 ± 8.6	<0.001
Fasting insulin, µIU/mL	18.7 (14.6–24.3)	7.4 (5.6–9.5)	<0.001
HOMA-IR	5.0 (3.8–6.4)	1.6 (1.2–2.0)	<0.001
Total cholesterol, mg/dL	197.8 ± 37.4	174.9 ± 30.2	<0.001
Triglycerides, mg/dL	178 (143–219)	113 (91–139)	<0.001
LDL-C, mg/dL	121.6 ± 31.5	103.2 ± 25.9	0.001
HDL-C, mg/dL	41.8 ± 8.7	50.9 ± 9.3	<0.001

Comparison of adipose endocrine function, redox balance, and metabolic enzyme activities between the study groups

The insulin-resistant obesity group exhibited significantly lower levels of adiponectin, SOD and GPx, and higher levels of leptin, resistin, MDA, ALT, AST and GGT as compared to healthy controls (all $P \leq 0.008$); see Table 3. The mean LDH level was slightly higher in the insulin-resistant group, but this difference was not significant ($P = 0.067$). These results suggest that there is adipokine imbalance, oxidative imbalance and mild hepatic metabolic disturbance.

Table 3. Adipokine, Oxidative-Stress, and Metabolic-Enzyme Profiles in Insulin-Resistant Obesity and Healthy Controls

Biomarker	Obesity with insulin resistance (n=100)	Healthy controls (n=50)	P value
Adiponectin, µg/mL	6.8 ± 2.1	10.9 ± 3.0	<0.001
Leptin, ng/mL	29.4 (21.8–38.7)	11.7 (8.1–16.0)	<0.001
Resistin, ng/mL	11.6 ± 3.5	7.9 ± 2.4	<0.001
MDA, µmol/L	4.6 ± 1.1	3.1 ± 0.8	<0.001
SOD, U/mL	7.2 ± 1.6	9.5 ± 1.9	<0.001
GPx, U/L	41.8 ± 8.6	50.6 ± 9.2	<0.001
ALT, U/L	29 (23–37)	22 (18–28)	<0.001
AST, U/L	24 (20–30)	21 (18–26)	0.008
GGT, U/L	32 (23–44)	21 (16–29)	<0.001
LDH, U/L	196 ± 35	185 ± 33	0.067

Spearman correlation analysis of circulating biomarkers and insulin-resistance severity among participants with insulin-resistant obesity

As presented in Table 4, HOMA-IR was positively related to leptin, resistin, MDA, ALT and GGT ($P \leq 0.029$) and inversely related with adiponectin, SOD and GPx ($P \leq 0.013$). Leptin had the highest positive correlation ($\rho = 0.414$) while adiponectin had the highest inverse correlation ($\rho = -0.392$). There was no significant correlation between AST, LDH and HOMA-IR ($P > 0.05$).

Table 4. Correlations of Adipokines, Oxidative-Stress Markers, and Metabolic Enzymes with HOMA-IR

Variable	Spearman's ρ with HOMA-IR	P value
Adiponectin	-0.392	<0.001
Leptin	0.414	<0.001
Resistin	0.309	0.002
MDA	0.361	<0.001
SOD	-0.281	0.005

GPx	-0.247	0.013
ALT	0.219	0.029
AST	0.143	0.156
GGT	0.271	0.006
LDH	0.118	0.242

Adjusted associations of adiposity, adipokines, oxidative-stress markers, and metabolic enzymes with insulin resistance

BMI, leptin, MDA, and GGT had independent positive association with HOMA-IR, whereas adiponectin and SOD had independent negative association (all $P \leq 0.032$), as shown in Table 5. The standardized effect for BMI was the largest ($\beta = 0.482$, $P < 0.001$). No association was found between HOMA-IR and resistin, age or sex ($P > 0.05$). That's just a cross-sectional correlation, and not evidence of cause and effect.

Table 5. Multivariable Predictors of HOMA-IR among Participants with and without Insulin-Resistant Obesity

Predictor	B coefficient	95% CI	Standardized β	P value
BMI, per 1 kg/m ²	0.180	0.130 to 0.230	0.482	<0.001
Adiponectin, per 1 μ g/mL	-0.140	-0.230 to -0.050	-0.181	0.003
Leptin, per 5 ng/mL	0.120	0.050 to 0.190	0.169	0.001
Resistin, per 1 ng/mL	0.051	-0.008 to 0.110	0.076	0.091
MDA, per 1 μ mol/L	0.240	0.080 to 0.400	0.148	0.004
SOD, per 1 U/mL	-0.090	-0.172 to -0.008	-0.101	0.032
GGT, per 10 U/L	0.100	0.019 to 0.181	0.091	0.016
Age, per year	0.008	-0.006 to 0.022	0.043	0.259
Male sex	0.112	-0.174 to 0.398	0.030	0.441

Discussion

In the present study, we have shown a coordinated disbalance in the adipose-tissue hormones, oxidative balance, glucose and lipid metabolism and hepatic enzymes in the patients with obesity associated insulin resistance. The differences in these biochemical parameters were not significant in age, sex, residence and smoking therefore, these differences are not likely to be attributable to these variables. On the other hand, the significantly higher BMI and WC of insulin-resistant group suggest high general and central adiposity. The higher prevalence of family history of type 2 diabetes is biologically plausible because the genetic susceptibility and common family lifestyle factors play a role in the determinants of adiposity, β -cell capacity and insulin sensitivity. Similarly, Aisike et al. found that the metabolically unhealthy obesity group had a higher waist circumference, blood pressure, dyslipidemia and HOMA-IR compared to the metabolically healthy groups [19]. This raised blood pressure in the present study could be associated with activation of the sympathetic nervous system, endothelial dysfunction, adipose renin-angiotensin-system activation, oxidative stress, and compensatory hyperinsulinemia.

The glycemic findings indicated that participants with obesity-associated insulin resistance had a higher fasting glucose level, fasting insulin level, and HOMA-IR. Given the relatively low fasting glucose level, the relatively low number of participants had reached an uncontrolled diabetes status, and many were in a prediabetic or early stage of

metabolic dysfunction. Sweis et al. showed that there was a tight association between adipokine imbalance and HOMA-IR among five African-origin populations, with the extent of the association being different for each population and metabolic phenotype [20]. Similarly, Wani et al. reported that insulin resistance and inflammation in adipose tissue was higher in metabolically unhealthy obesity than in metabolically healthy obesity [21]. Such results are consistent with the notion that a state of compensatory hyperinsulinemia can help to regulate the glucose levels near normal for a while until the β -cell function deteriorates and is accompanied by a chronic hyperglycemia.

The higher total cholesterol, triglycerides and LDL-C and lower HDL-C levels found in the insulin-resistant group is the atherogenic lipid profile found in impaired insulin action. Increased insulin resistance raises circulating free fatty-acid delivery to the liver, and increases the lipolysis of fat and the production of very-low-density lipoprotein. Hyperinsulinemia also contributes to a change in the activity of lipoprotein lipase and a decrease in the clearance of triglyceride-rich lipoprotein (TRL). This leads to exchange of triglycerides between lipoproteins, leading to the formation of triglyceride-enriched HDL particles that are quickly removed, thus accounting for the reduced HDL-C. This is consistent with the work of Primo et al. which correlated risk of metabolic syndrome in female obesity to hyperglycemia, hyperinsulinemia, insulin resistance and lipid abnormalities [22].

The levels of serum adiponectin were significantly decreased while those of leptin and resistin were increased in participants with IR, which was associated with obesity. The findings were similar to those reported by Aisike et al, who recorded a decrease in adiponectin levels and an increase in leptin in metabolically unhealthy obesity [23]. The loss of adiponectin could result in a decrease in the ability of AMP-activated protein kinase signaling, fatty-acid oxidation, glucose uptake and inhibition of hepatic gluconeogenesis. Conversely, higher leptin levels are likely to be associated with higher amounts of body fat and peripheral and central leptin resistance. Therefore, the positive correlation of leptin with HOMA-IR and the negative correlation of adiponectin with HOMA-IR is complementing evidence of adipocyte dysfunction. Recent studies also have revealed that the ratio of leptin to adiponectin has been shown to be closely associated with HOMA-IR, but this association is different in various ethnic groups and among men and women [24]. Sex hormones, fat distribution, menopausal status, assay characteristics and the presence or absence of diabetes in the sample may contribute to the differences.

Resistin was elevated in the insulin-resistant group, and was positively and to a lesser extent correlated with HOMA-IR. It is consistent with the finding of Primo et al. that showed the association between a resistin-based index and metabolic syndrome in obese women [25]. Al-Dallal et al. however, found that the association of resistin with obesity and metabolic health were modulated by sex and population characteristics and were not invariably similar across the analyses [26]. The difference could represent an important difference in the biology of resistin in humans versus experiments. In humans, resistin is mainly secreted by monocytes/macrophages and not by mature adipocytes, so plasma levels of resistin may be an indicator of activation of inflammatory cells rather than adipocyte mass. Measured levels of resistin may also be affected by ethnicity, renal clearance, infection, medications, analytical platforms and RETN polymorphisms.

Oxidative-stress profile was manifested as the elevation of MDA and the decrease of SOD and GPx activities. MDA is a marker of lipid peroxidation, and may be a sign of oxidative damage to polyunsaturated lipids in membranes, while SOD and GPx are important enzyme defence mechanisms against the superoxide radicals and hydrogen peroxide. Jakubiak et al. identified obesity-insulin-resistance component of metabolic syndrome of which systemic oxidative-stress indicators were especially strongly related [27]. Likewise, in the obese population, a meta-analysis found that antioxidant supplementation lowered the levels of MDA and resulted in small changes in fasting

glucose and HOMA-IR [28]. The observations presented here support the notion that there is a bi-directional relationship: an excess of nutrients stimulates the production of ROS in the mitochondria and ROS, in turn, is associated with decreased insulin-receptor substrate and PI3K–Akt signaling.

However, other studies have failed to show decreased antioxidant-enzyme activity in obesity. In some investigations, activity levels of SOD or GPx have been reported as being increased and this was considered to be an early compensatory response to the enhanced production of reactive-oxygen-species [29]. Longer or more severe metabolic stress, however, may deplete the antioxidant defence or lead to an oxidative modification of antioxidant enzymes, resulting in the lower activities found here. The apparently conflicting results may thus be due to differences in the duration of obesity, the antioxidant intake in the diet, the micronutrient status, age, tissue examined, and determination of activity in serum, erythrocytes, or adipose tissue.

The insulin-resistant group had moderately increased levels of ALT, AST and GGT; there was no significant difference in LDH levels. The small elevation of the aminotransferases is compatible with low grade hepatic metabolic stress, not with severe hepatocellular injury. Similarly, Jalili et al. noticed positive correlation between obesity and ALT and GGT serum levels, but the correlation was different for each enzyme [30]. Villasis-Keever et al. also found that the levels of aminotransferase are higher in obese adolescents with insulin resistance than in those without insulin resistance [31]. In addition, simple insulin resistance indices have been linked to higher steatosis, liver stiffness and biochemical abnormalities in overweight/obese people with metabolic fatty liver disease [32].

Adjustment for this had no significant effect on the bivariate correlation of GGT with HOMA-IR, but did significantly affect the bivariate correlation for AST and LDH. GGT could be more metabolically informative as it also involves extra cellular metabolism of glutathione and may be useful as an indicator of hepatic fat, oxidative stress and cardiometabolic dysfunction. In middle-aged adults, Zheng et al. found that GGT was more closely associated with diabetes than was ALT or AST [33]. Moreover, if GGT levels are normalized during follow-up, weight loss, decrease in triglyceride and improvement in HOMA-IR has been linked to a patient with fatty liver disease [34]. But, there have been some studies that have shown higher correlations with ALT [35]. These variations can be attributed to alcohol consumption, sex ratio, hepatic steatosis, drug exposure, lab reference ranges, and lack of known liver disease.

Amongst the parameters included in the multivariable model, BMI was the strongest independent correlate of HOMA-IR, whereas adiponectin, leptin, MDA, SOD, and GGT had smaller independent associations. It appears that adiposity is still the most important factor, but endocrine dysfunction, oxidative imbalance, and hepatic stress provide information in addition to BMI. A recent study of circulating DKK1 demonstrated that a mediator associated with obesity could simultaneously act on both domains, oxidative stress and insulin signalling, supporting a mechanistic interaction between these domains [36]. After adjustment for body composition, Asprosin has also been linked to insulin resistance and indices for oxidative stress [37]. Structured exercise intervention studies which have demonstrated decreases in resistin and HOMA-IR provide further evidence that these biomarkers are not fixed characteristics but are modifiable.

The adjusted R^2 of 0.589 shows that the model accounted for an important but partial amount of the variability of the HOMA-IR. Factors that could contribute to residual variation include diet, physical activity, sleep, distribution of visceral to subcutaneous fat, genetic susceptibility, inflammatory mediators, hepatic fat, and medications. The absence of independent significance of resistin does not imply lack of biological relevance, but rather its association with BMI, leptin, MDA and inflammatory activity are likely to have been confounded by shared variance. Also, the age and sex were not independently

associated after adjustment which may be due to the relatively small age range and acceptable sex ratio [39].

4. Conclusion

In conclusion, the results corroborate an integrated immunometabolic model in which adipocyte dysfunction, oxidative stress, dyslipidaemia and liver metabolic dysfunction are associated with insulin resistance. There is a lack of temporal order and causality, however, in the case-control and cross sectional design. HOMA-IR is also an indirect measure, not a hyperinsulinemic – euglycemic clamp measurement. Further prospective analyses should include external model validation, repeated measurements of biomarkers, dietary and physical-activity assessment, as well as imaging-based visceral and hepatic-fat assessment. Ultimately, multi-marker evaluation might be more informative than any single analyte for identifying metabolically high-risk obesity.

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