ORIGINAL ARTICLE

Immunological Role of Soluble CD163 and CD248 Biomarkers in Insulin Resistance among Healthy Iraqi Adults

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ABSTRACT

Background: *Insulin resistance (IR) is a major metabolic disturbance with associations with inflammation and impaired glucose homeostasis. Soluble CD163 and soluble CD248 are stroma- and macrophage-derived molecules that could bridge immune activation and insulin resistance.* ***Objective:*** *The present study was conducted to identify the serum levels of sCD163 and sCD248, and their association with insulin resistance in apparently healthy Iraqi adults.* ***Methodology:*** *A cross-sectional study was undertaken on 98 euglycemic non-diabetic adults (≥45 years). Participants were categorized according to HOMA-IR values (≤3 = insulin-sensitive, >3 = insulin-resistant). Anthropometric and biochemical parameters were measured, and serum concentrations of sCD163 and sCD248 were determined with ELISA kits.* ***Results:*** *Insulin resistance was present in 25 patients (25.5%). Both sCD163 and sCD248 concentrations were higher in IR individuals than in insulin-sensitive individuals ($p < 0.05$). Both biomarkers were found to be positively correlated with HOMA-IR and fasting insulin, indicating their implication in metabolic inflammation.* ***Conclusion:*** *Elevated serum sCD163 and sCD248 can serve as an early immunological indicator of insulin resistance in apparently healthy individuals. Monitoring them might be helpful in identifying subclinical metabolic risk.*

INTRODUCTION

Type 2 diabetes mellitus (T2DM) continues to be a global public-health challenge in spite of ongoing advancements in its management. Insulin resistance (IR), i.e., a diminished biological response to insulin in key target tissues such as the liver, skeletal muscle, and adipose tissue, is considered the primary pathophysiological feature of T2DM and a variety of metabolic disorders[1]. This defect in insulin action is accountable for defective glucose uptake, compensatory hyperinsulinemia, and long-term metabolic dysregulation[2].

Although classical risk factors such as obesity, sedentary lifestyle, and genetic predisposition are well established, recent evidence suggests that immune and inflammatory mechanisms also play a central role in the development of IR[3]. Chronic low-grade inflammation mediated by macrophage activation within adipose tissue contributes to the disruption of insulin-signaling pathways[4].

Among the immune-related molecules, soluble CD163 (sCD163) and soluble CD248 (sCD248) have received attention as novel biomarkers linking immune activation and metabolic dysfunction. sCD163 is a macrophage-specific scavenger receptor shed into the circulation during macrophage activation. Elevated sCD163 levels have been reported in obesity, metabolic syndrome, and hepatic insulin resistance, supporting its role as a macrophage-derived marker of metaflammation[5,6].

Similarly, CD248 (endosialin) is a transmembrane glycoprotein expressed on stromal and adipose-tissue cells, involved in extracellular-matrix interactions and angiogenesis. Recent evidence has shown that CD248 can directly bind to the insulin receptor and attenuate its autophosphorylation, thereby promoting insulin resistance[7].

Understanding the relationship between these immunological biomarkers and IR could provide new insight into the mechanisms linking inflammation and metabolism and may help identify novel therapeutic or diagnostic targets in early metabolic dysfunction among apparently healthy individuals. Therefore, the aim of the present study was to investigate the association between serum levels of soluble CD163 (sCD163) and soluble CD248 (sCD248) and insulin resistance among apparently healthy adults, to explore their potential roles as early immunometabolic biomarkers in the pathogenesis of type 2 diabetes mellitus (T2DM.

METHODOLOGY

Study Design and Population

This cross-sectional study was conducted on ninety-eight apparently healthy adults of Arab ethnicity (both sexes), aged ≥ 45 years. All participants were euglycemic and non-diabetic, defined by glycated hemoglobin (HbA1c ≤ 5.7%). The study was carried out between October 2024 and May 2025. Subjects were recruited from employees of several universities in Baghdad, Iraq, who voluntarily agreed to participate after signing informed consent forms.

Individuals with diabetes mellitus, cardiovascular, renal, or hepatic disorders, as well as those using lipid-lowering agents, corticosteroids, or medications known to influence insulin resistance, were excluded. Pregnant or lactating women and those receiving oral contraceptives or hormonal replacement therapy were also excluded.

Anthropometric and Clinical Measurements

Demographic details like sex and age were collected under face-to-face interview. Weight in kilograms and height in meters were measured using standard technique, while body mass index (BMI) was calculated using weight (kg)/height (m^2). Waist and hip circumferences (WC and HC) were measured to obtain waist-to-hip ratio (WHR). These were collected by field staff using calibrated equipment.

Sample Collection and Laboratory Analyses

After overnight fasting (a minimum of 8 hours), 5 mL of venous blood was taken from each volunteer in the morning. Serum was kept at −20 °C and analyzed afterwards.

Biochemical markers including fasting blood glucose (FBG), lipid profile (total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C)), fasting insulin, and HbA1c were determined by employing commercial diagnostic kits according to the manufacturer's guidelines (Sunlog, China).

Insulin resistance was estimated using the homeostasis model assessment for insulin resistance (HOMA-IR), calculated as:

$$\frac{\text{Fasting glucose (mg/dL)} \times \text{Fasting insulin (μU/mL)}}{405} = \text{HOMA-IR}$$

Based on previous validation studies, a HOMA-IR value > 3.0 was considered indicative of insulin resistance[8,9].

Determination of Serum sCD163 and sCD248

Serum concentrations of soluble CD163 and CD248 were measured using quantitative sandwich enzyme-linked immunosorbent assay (ELISA) kits (Sunlog, China). Procedures were strictly followed in accordance with the protocol from the manufacturer. Essentially, standards and diluted serum samples were pipetted into pre-coated wells to the volume of 100 µL and incubated for 2 hours at 37 °C. Washing was done after which biotin-conjugated antibodies were added and incubated with HRP-avidin conjugate and substrate (TMB). The reaction was halted and read for absorbance at 450 nm using a microplate reader. Concentrations were calculated from standard curves.

Statistical Analysis

SPSS software version 25 (IBM Corp., Chicago, IL, USA) was used for data analysis. Continuous values were reported as mean ± SD, and categorical values as percentages and counts. Group means were contrasted using the Student's t-test, and the chi-square test was used in the instance of categorical values. Pearson's correlation coefficient (r) was used for establishing relationships between sCD163, sCD248, and metabolic parameters. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Prevalence of Insulin Resistance

Among the 98 apparently healthy participants, 25 individuals (25.5%) were identified as having insulin resistance (IR) based on HOMA-IR > 3.0, whereas 73 (74.5%) were insulin-sensitive (IS).

Association of Demographic Factors with Insulin Resistance

Table 1 summarizes the demographic and anthropometric characteristics of the study population. Participants with IR were significantly older (56.52 ± 10.57 years) compared to the IS group (50.81 ± 8.42 years; p = 0.007). Body mass index (BMI) and waist-to-hip ratio (WHR) were also higher among IR subjects (28.52 ± 3.09 kg/m^2 and 0.93 ± 0.03, respectively) compared with IS individuals (26.94 ± 2.8 kg/m^2 and 0.90 ± 0.06; p = 0.019 and 0.011, respectively). No significant sex difference was observed (p = 0.133).

Lipid Profile and Insulin Resistance

All lipid profile parameters demonstrated significant differences between the groups (Table 2). Subjects with IR had higher levels of total cholesterol (174.8 ± 32.06 mg/dL), LDL-C (102.83 ± 23.47 mg/dL), and triglycerides (156.2 ± 37.18 mg/dL) compared with IS subjects (158.74 ± 27.79 mg/dL, 90.33 ± 21.53 mg/dL, and 131.21 ± 25.94 mg/dL, respectively). Conversely, HDL-C levels were significantly lower in the IR group (45.12 ± 5.4 mg/dL) than in IS individuals (47.37 ± 4.29 mg/dL; p = 0.038).

Glycemic and Insulin-Related Parameters

Table 3 presents glycemic indices and insulin-related markers. Individuals with IR had significantly higher fasting blood glucose (92.52 ± 6.71 mg/dL vs 87.03 ± 4.87 mg/dL; p = 0.031), HbA1c (5.22 ± 0.37 % vs 4.85 ± 0.27 %; p = 0.026), fasting insulin (12.38 ± 1.92 µU/mL vs 10.35 ± 1.72 µU/mL; p < 0.001), and HOMA-IR (3.58 ± 0.33 vs 2.20 ± 0.51; p < 0.001).

Table1: Demographic and anthropometric characteristics associated with insulin resistance.

Parameter	Insulin Resistance		p-value
	Yes (n=25)	No (n=73)	
Age (years) Mean±SD Range	 56.52± 10.57 40-82	 50.81±8.42 40-72	0.007
Sex Males Females	 8(32%) 17(68%)	 36(49.32%) 37(50.68%)	0.133
Waist Circumference (cm) Mean±SD Range	 90.4±8.16 74-100	 87.62±7.71 70-102	0.128
Hip circumference (cm) Mean±SD Range	 96.28±5.61 83-104	 95.66±5.87 80-105	0.645
Body Mass Index (Kg/m^2) Mean±SD Range	 28.52±3.09 21.67-32.2	 26.94±2.8 21.67-34.6	0.019
Waist/Hip Ratio Mean±SD Range	 0.93±0.03 0.85-0.99	 0.90±0.06 0.77-0.98	0.011

Values are presented as mean ± SD or n (%); $p < 0.05$ considered significant.

Table 2: Lipid profile parameters in insulin-resistant and insulin-sensitive subjects.

Parameter	Insulin Resistance		p-value
	Yes (n=25)	No (n=73)	
Total Cholesterol, mg/dL Mean±SD Range	 174.8±32.06 113-249	 158.74±27.79 106-239	0.018
HDL, mg/dL Mean±SD Range	 45.12±5.4 38-62.1	 47.37±4.29 39-59	0.038
LDL, mg/dL Mean±SD Range	 102.83±23.47 69-151	 90.33±21.53 50-149	0.016
Triglyceride, mg/dL Mean±SD Range	 156.2±37.18 93-228	 131.21±25.94 89-213	<0.001

Values are expressed as mean ± SD; $p < 0.05$ considered statistically significant.

Table 3: Glycemic and insulin-related parameters in IR and IS groups.

Parameter	Insulin Resistance		p-value
	Yes (n=25)	No (n=73)	
FBG, mg/dL Mean±SD Range	 92.52±6.71 81-106	 87.03±4.87 78-99	0.031
HbA1c level, % Mean±SD Range	 5.22±0.37 4.4-5.7	 4.85±0.27 4.2-5.5	0.026
Fasting Insulin, µU/mL Mean±SD Range	 12.38±1.92 7.7-15	 10.35±1.72 7.3-14	<0.001
HOMA-IR Mean±SD Range	 3.58±0.33 3.1-4.02	 2.2±0.51 1.17-3.06	<0.001

Values are expressed as mean ± SD; $p < 0.05$ considered statistically significant.

Serum Levels of sCD163 and sCD248

As shown in Figure 1, the mean serum level of sCD163 was significantly higher in the IR group (518.26 ± 124.1 ng/mL) than in IS participants (450.25 ±125.33 ng/mL; $p < 0.05$). Similarly, Figure 2 demonstrates that serum sCD248 was also elevated among IR individuals (182.26 ± 44.43 pg/mL) compared with IS subjects (154.92 ± 42.77 pg/mL; $p < 0.05$).

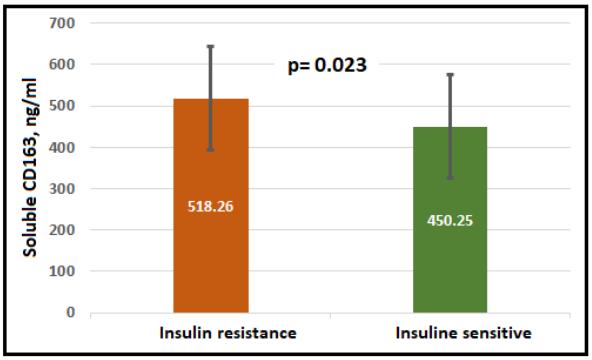

Fig. 1: Mean serum levels of soluble CD163 in insulin-resistant and insulin-sensitive groups

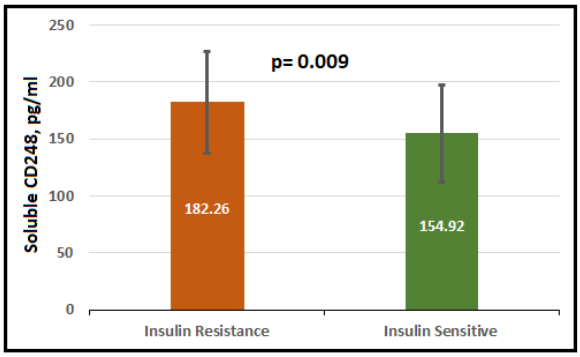

Fig. 2: Mean serum levels of soluble CD248 in insulin-resistant and insulin-sensitive groups.

Correlation Analyses

Pearson's correlation test showed that sCD163 correlated positively with fasting insulin ($r = 0.306$; $p = 0.004$) and HOMA-IR ($r = 0.225$; $p = 0.034$). Similarly, sCD248 displayed positive correlations with HbA1c ($r = 0.261$; $p = 0.012$), HOMA-IR ($r = 0.243$; $p = 0.022$), and sCD163 ($r = 0.269$; $p = 0.035$) (Table 4).

To comply with EJMM guidelines (maximum 7 tables/figures), all correlation scatter plots were merged into one composite figure (Figure 3) containing five panels:

(A) sCD163 vs fasting insulin; (B) sCD163 vs HOMA-IR; (C) sCD163 vs sCD248; (D) sCD248 vs HbA1c; (E) sCD248 vs HOMA-IR

Table 4: Correlation of serum sCD163 and sCD248 with demographic, lipid, and glycemic parameters.

Variable	CD163		CD248	
	r	p-value	r	p-value
Age	-0.085	0.427	0.061	0.569
BMI	0.250	0.018	0.037	0.730
Waist circumference	0.142	0.456	0.188	0.078
Hip circumference	-0.178	0.347	0.153	0.418
WHR	0.067	0.535	0.034	0.752
TC	0.069	0.522	0.033	0.762
TG	0.142	0.456	0.052	0.785
HDL	-0.163	0.126	-0.115	0.282
LDL	0.155	0.413	0.153	0.418
FBS	-0.017	0.872	0.019	0.857
Fasting insulin	0.306	0.004	0.103	0.355
HbA1c	0.044	0.682	0.261	0.012
HOMA-IR	0.225	0.034	0.243	0.022
CD163			0.269	0.035

Values represent Pearson's correlation coefficients; $p < 0.05$ considered statistically significant.

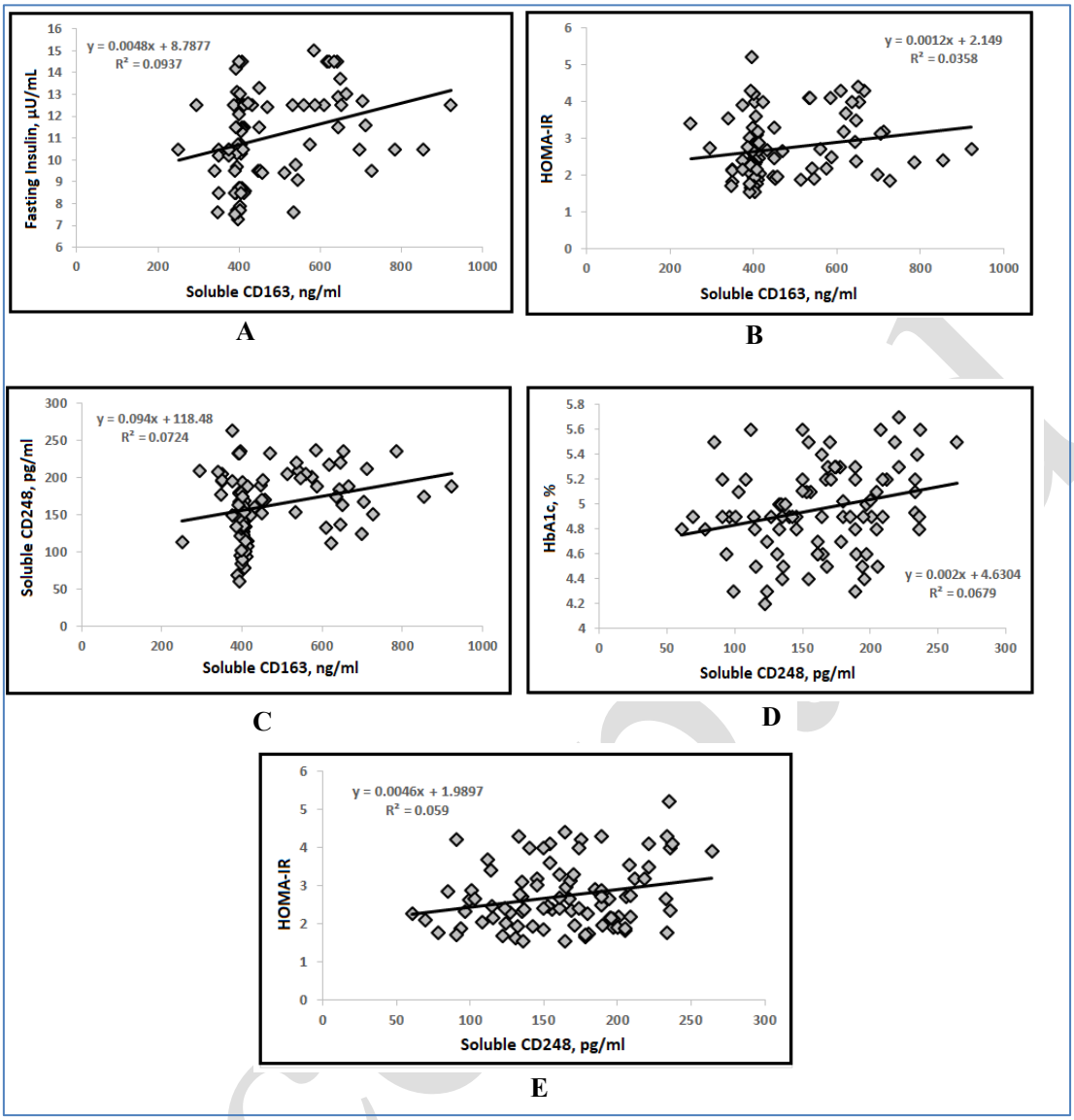

Fig. 3: Composite correlation plots of soluble CD163 and CD248 with selected metabolic parameters
(A) sCD163 vs fasting insulin; (B) sCD163 vs HOMA-IR; (C) sCD163 vs sCD248; (D) sCD248 vs HbA1c; (E) sCD248 vs HOMA-IR.

DISCUSSION

In this cross-sectional cohort of apparently healthy Iraqi adults, circulating sCD163 and sCD248 levels were significantly higher among individuals with insulin resistance (IR) and both biomarkers correlated with HOMA-IR and glycemic indices. These findings highlight an immuno-metabolic interaction in which macrophage activation and stromal remodeling contribute to the impairment of insulin signaling, in agreement with previous studies describing immune-mediated mechanisms in IR [10-12].

Our results confirm that sCD163 (a marker released by activated macrophages) is strongly associated with IR and the metabolic syndrome[13,14]. Similar findings were reported by Kazankov et al., who demonstrated that sCD163 reflects hepatic inflammation, fibrosis, and insulin resistance in obese subjects[15]. Furthermore, Grannes et al.[16] proved that liraglutide treatment decreased circulating sCD163 significantly, confirming the biomarker's dynamic response to metabolic improvement.

The elevated levels of serum sCD248 demonstrated in the present study also support the role of stromal and extracellular-matrix pathways in the regulation of metabolism. Benedet et al. have demonstrated recently that CD248 physically interacts with the insulin receptor and reduces its autophosphorylation, hence impairing downstream insulin signaling[17]. These molecular findings suggest that high sCD248 levels can be a mechanistic link between activated stroma and reduced insulin sensitivity. In addition, Nguyen[10] and Plevriti et

al.[18] recognized the growing significance of CD molecules, including CD248, as primary immune regulators of metabolic disease[10,18].

The lipid profile results (elevated TC, LDL-C, TG and low HDL-C in IR patients) are in line with typical dyslipidemic dysfunctions that occur with insulin resistance and concur with large population research establishing the effectiveness of triglyceride/HDL-C ratio as an easy marker for IR among Iraqi adults[19,20].

Combining, these findings support the potential usefulness of sCD163 and sCD248 as early immune biomarkers for detection of subclinical insulin resistance. sCD163 appears to mirror macrophage-driven inflammation, and sCD248 may serve to signal stromal suppression of insulin receptor function. Combining these immune markers with lipid-derived indices (e.g., TG/HDL-C ratio) may improve early metabolic risk stratification and target candidates for targeted interventions such as GLP-1 receptor agonists that target macrophage and stromal function[16,17].

CONCLUSIONS

This study provides evidence that elevated serum soluble CD163 and CD248 levels are associated with insulin resistance in apparently healthy adult Iraqi patients. Their positive correlation with fasting insulin, HbA1c, and HOMA-IR indicates that macrophage activation as well as stromal dysregulation is involved in early metabolic impairment.

sCD163 probably reflects low-grade inflammatory processes in liver and fat tissues, whereas sCD248 could be a marker of dysregulated stromal-insulin receptor interaction decreasing insulin action. They are collectively new immunologic markers of subclinical insulin resistance.

Combine these biomarkers with usual biochemical measures, e.g., triglyceride-to-HDL-C ratios, so that risk detection may be improved at an early stage in populations at risk of metabolic disease. Interventional and longitudinal studies in the future are recommended to evaluate their predictive value and to ascertain the impact of modulation of such immune mechanisms through lifestyle or drugs.

Ethical Approval

The study protocol was reviewed and approved by the Scientific and Ethical Committee of the College of Science, University of Tikrit, Iraq.

Declarations:

Consent for publication: Not applicable

Availability of data and material: Data are available upon request.

Competing interests: The author(s) declare no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

This manuscript has not been previously published and is not under consideration in another journal.

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