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# Soluble CD36 Concentration in Diabetic Hypertensive Patients with Coronary Atherosclerosis

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**ABSTRACT**

Atherosclerosis is a chronic condition defined by cholesterol retention and arterial wall inflammation. CD36 is indeed a membrane protein found in the monocyte-macrophage systems and endothelial cells involved in the cellular uptake of oxidized low-density lipoproteins and long-chain fatty acids with a crucial role in the pathophysiology of atherosclerosis. The purpose of this research is to compare the diagnostic usefulness of soluble CD36 (sCD36) to high sensitivity C reactive protein (hs-CRP) in diabetic hypertensive individuals with coronary atherosclerosis and the correlation between these parameters in research groups. One hundred individuals with coronary atherosclerosis were divided into four groups based on diabetes mellitus (DM) and/or hypertension (HTN), with 100 participants with routine angiography serving as a control group. The serum levels of sCD36 and hs-CRP were quantified using a sandwich enzyme-linked immunosorbent assay (ELISA) for sCD36 and a particle-enhanced immune turbidimetric assay for hs-CRP, respectively. A study group's lipid profiles, hematological markers, and clinical aspects were compared. Compared to the control, sCD36 and hs-CRP levels in patients increased considerably ($p<0.05$). The sCD36 level varied substantially between groups ($p<0.05$), with the DM-HTN group having the highest sCD36 level among the patient groups. Further, the hs-CRP level indicated a significant difference among patients and controls ($p<0.05$). CD36 correlated significantly and positively with the following terms BMI, hs-CRP, Total cholesterol and non-HDL-C ($p<0.05$).

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## Introduction

Atherosclerosis contributes to cardiovascular disorders, including ischemic heart disease and stroke. The pathogenesis of this complicated multifactorial illness is chronic and progressive, with fat accumulation, low-grade inflammation in the walls of large and medium-sized arteries, and endothelial dysfunction (1). Cholesterol deposition and chronic inflammation are two crucial components in the pathophysiology of atherosclerosis (2). Atherosclerosis comprises three distinct stages: fatty streak production, atheroma induction, and atherosclerotic plaques (3). The topic of diabetes mellitus as a concomitant disease that frequently confounds hypertension considerably increases total morbidity and mortality (4).

Based on a 2017 consensus among experts in the area, the CD36 is a sort of B scavenger receptor that is also known as SCARB3, fatty-acid translocator (FAT), glycoprotein 4 (GPIV), and a scavenger receptor class B protein (SR-B2) (5). CD36 functions as a long-chain fatty acid (FA) translocator (6), facilitating the transfer of native and oxidized lipids in cells (7). A soluble version of CD36 was recently discovered in cell-free plasma. They found elevated plasma levels of sCD36 in diabetic patients, which were tightly linked with insulin resistance (8), possibly released into the circulation as low-grade inflammation part in insulin resistance. The researchers hypothesized that sCD36 could indicate plaque instability based on lipid metabolism, inflammation, and platelet activation.

The elevation of lipoprotein level in the body of hyperlipidemia patients causes vascular endothelial function impairment and the changes in the surface property of endothelial cells, monocytes, and lymphocytes (9), promoting the adherence of monocytes to vascular endothelial cells. Additionally, macrophages are transformed into macrophage foam cells through a scavenger receptor's phagocytosis of oxidized low-density lipoprotein (Ox-LDL), ultimately forming atherosclerotic lipid stripes (10).

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As the scavenger receptor B family (11), sCD36 physiologically mediates the Ox-LDL phagocytosis by macrophages. It promotes foam cell formation in the body, which is considered the core factor for atherosclerosis (12).

Several large prospective trials have demonstrated that the inflammatory biomarker hsCRP is a reliable predictor of future cardiovascular events (13). Numerous investigations from Europe and the US show that increased hsCRP levels in otherwise healthy men and women are a good predictor of future cardiovascular events (14). When combined with other risk factors, hsCRP works as a substantial independent predictor of cardiometabolic risk(15). hsCRP is an independent significant predictor and risk factor of cardiometabolic risk, with additive value to metabolic syndrome elements (16).

**Materials and methods**

The study population included 100 consecutive subjects enrolled in this case-control research, referred to the surgical specialty hospital-cardiac center's emergency department in Erbil-Iraq, for primary percutaneous coronary intervention (PCI) from Jan 2020 to Mar 2020.

All patients had their initial coronary angiography (COA), and those who did not have an artery blockage were eliminated from the research. Furthermore, patients with congenital heart disease, heart failure, cardiomyopathy, pericarditis, myocarditis, severe valvular heart disease, latest surgeries or traumas, active inflammatory or autoimmune diseases, malignancies, and bleeding and clotting problems were excluded from the work.

Participants were classified as follows based on their history of diabetes and/or hypertension:

i. Cases without DM and HTN
ii. cases with DM without HTN
iii. Cases with HTN without DM
iv. Cases with DM and HTN

The control group consisted of 100 people who were angiographically confirmed to have normal coronary arteries, had chest pain that was not attributable to a cardiac cause, and showed no obvious significant signs of lung alteration. This group of people did not have diabetes or obesity.

The medical ethics committee of Hawler Medical University's College of Medicine certified the research project. During personal interviews, information about the patient's medical history was gathered using specifically created questionnaires. Diabetic patients were diagnosed based on a history of DM, whether they had been treated with or without anti-diabetic medicines, and were proven to have a hemoglobin A1c (HbA1c) level >6.5% (17). Similarly, HTN (≥140/90 mmHg) was confirmed based on one of the parameters of the previous diagnosis, current use of antihypertensive medicines, and repeated blood pressure measurements at least 2-3 times under stable settings. The conventional method for determining the body mass index was weight (kg)/height m2 (BMI). Coronary angiography was conducted on the right femoral artery for all research groups, i.e., patients and controls, as a conventional procedure for determining if the route was normal or diseased, only achieved for those admitted for various reasons (e.g., atherosclerotic coronary artery disease, chest pain). Participants in the control group experienced chest pain but were found to have normal coronary arteries by angiography (no lesions). Several other causes can be the source of the chest pain, such as psychological factors such as severe sadness and extreme stress; however, we were only concerned if the patient was free of chest pain connected to cardiac origin and no other causes. All patients received loading doses of aspirin (300 mg) and clopidogrel (300-600 mg) or were reloaded with ticagrelor 180 mg before the angiography process and with heparin before PCI for patients who were verified to have a new arterial blockage. Diagnostic and guiding catheters were inserted through a 6 French femoral sheath to access the coronary sinuses.

PCI was performed on all subjects who had a new arterial occlusion. COA results were used to identify the location of the culprit lesions and the number (1, 2, or 3) of the damaged vessel(s). Blood samples were obtained from all subjects immediately after admission and before COA using the venipuncture procedure. Serum was extracted from the blood and stored at -80°C for future examination. All individuals had baseline laboratory investigations, including biochemical and hematological testing.

The serum sCD36 level was quantified using a human sCD36 ELISA kit (MyBioSource, USA). The particle enhanced immunoturbidimetric assay determined hs-CRP (Roche Diagnostics GmbH)

concentrations using Cobas c111. The Cobas c111 (Roche Diagnostics GmbH) was used to analyze HbA1c and lipid profiles, and the Swelab Alpha Coulter Analyzer was used to determine the total blood count (Swelab, Sweden). SPSS Statistics 26.0 was used to perform statistical analysis on the data. The constant variables in the groups were defined as mean ± SE. The one-way analysis of variance (ANOVA) was performed for multiple comparisons. The Student's t-test and the Mann–Whitney U test were used to compare the two continuous parameters. A chi-squared test was also used to examine categorical variables. Pearson's correlation coefficient was used to determine the association between sCD36 and hs-CRP and the correlation between the two markers and other research parameters. At P<0.05, the P-value was declared significant.

## Results and discussion

As shown in Table 1, the levels of sCD36 and hs-CRP in patients considerably increased compared with the control groups (P<0.05). Furthermore, the elevated levels of low-density lipoprotein–cholesterol (LDL-C), TC/HDL, BMI, and HbA1c significantly differed (P>0.05) between the groups mentioned above. No statistically significant differences were observed in diastolic blood pressure (DBP), leukocytes, HDL-C, cholesterols, or triglycerides between the patients and the controls (P>0.05). Referring to the COA findings, the majority of patients had one damaged vascular, with the left anterior descending artery (LAD) being the most commonly affected artery, followed by the left circumflex (LCX) and the right coronary artery (RCA).

**Table 1.** Baseline characteristics of coronary atherosclerosis in patients and controls

| Variables | Patient | Control | p |
|---|---|---|---|
| Age (years) | 37-85 | 33-76 | - |
| Male (%) | 63(63) | 46(46) | 0.015* |
| Smokers (%) | 35(35) | 29(29) | 0.363 |
| Diabetic (%) | 46(46) | 21(21) | 0.008** |
| Hypertension (%) | 50(50) | 29(29) | 0.004** |
| SBP (mmHg) | 132.30±1.86 | 122.025±0.34 | 0.001** |
| DBP (mmHg) | 80.85 ±0.72 | 79.95±0.25 | 0.421 |
| BMI ($Kg/m^2$) | 31.42±0.82 | 27.86±1.07 | 0.001** |
| HbA1c% | 7.03±0.21 | 5.15±0.03 | 0.001** |
| Inflammatory biomarkers | | | |
| sCD36(ng/ml)*** | 0.97±0.43 | 0.77±0.34 | 0.048* |
| hsCRP (mg/l) | 2.90±0.07 | 2.06±0.06 | 0.001** |
| Lipid profile and lipid ratios | | | |
| Total cholesterol (mg/dl) | 167.43±2.65 | 161.68±2.33 | 0.106 |
| Triglyceride (mg/dl) | 126.40±3.73 | 120.00±2.93 | 0.179 |
| HDL-C (mg/dl) | 39.57±0.81 | 41.40±0.77 | 0.103 |
| LDL-C (mg/dl) | 68.59±3.30 | 60.01±2.77 | 0.048* |
| Non-HDL (mg/dl) | 127.86±2.87 | 120.28±2.53 | 0.040* |
| Total cholesterol /HDL ratio | 4.29±0.11 | 3.99±0.09 | 0.033* |
| LDL/HDL ratio | 1.73±0.07 | 1.45±0.09 | 0.018* |
| Hematological index | | | |
| Leukocyte count ($10^3/\mu L$) | 7.04±0.13 | 6.83±0.87 | 0.187 |
| Angiographic findings (%) | | | |
| One vessel | 52 (52) | - | |
| Two vessels | 18 (18) | - | |
| Three vessels | 30 (30) | - | |
| Location of Culprit lesion (%) | | | |
| LAD | 50 (50) | - | |
| RCA | 17 (17) | - | |
| LCX | 33 (33) | - | |
| Medications (%) | | | |
| Aspirin (%) | 10 (10) | - | |
| Ticagrelor (%) | 9 (9) | - | |
| Clopidogrel (%) | 12 (12) | - | |
| Tablets or insulin injection (%) | 32 (32) | - | |
| Betablocker (%) | 27 (27) | - | |
| Statin (%) | 22 (22) | - | |

Values are expressed as mean±SE and n (%) for constant (t-test) and categorical variables, and Mann–Whitney U test. ***

**Table 2.** Serum mean concentrations of inflammatory indicators and other variables in coronary atherosclerosis groups as compared to controls

| Variables | Patient | | | | Control | P-Value |
|---|---|---|---|---|---|---|
| | Non-DM Non-HTN n 30 (30%) | DM only n 20 (20%) | HTN only n 24 (24%) | DM-HTN n 26 (26%) | Non-DM Non-HTN n 59 (59%) | |
| Age (yr) | 60.23±1.53[a] | 60.34±1.40[a] | 60.79±1.42[a] | 62.27±1.65[a] | 45.32±0.87[b] | 0.001** |
| SBP (mmHg) | 129.45±2.44[a] | 134.60±3.52[a] | 136.44±3.08[a] | 137.50±4.59[a] | 122.45±0.45[b] | 0.001** |
| DBP (mmHg) | 79.45±0.90[a] | 81.05±1.26[a] | 82.50±1.33[ab] | 83.31±1.82[a] | 80.00±0.20[a] | 0.223 |
| BMI (Kg/m$^2$) | 29.74±1.33[a] | 29.44±0.81[a] | 29.51±±0.96[a] | 30.54±1.03[a] | 25.40±0.83[b] | 0.001** |
| HbA1c% | 6.76±0.30[a] | 7.80±0.34[a] | 7.45±0.33[a] | 7.86±0.41[ab] | 5.19±0.20[c] | 0.001** |
| Inflammatory biomarkers | | | | | | |
| sCD36(ng/ml) | 1.04±0.66[a] | 1.17±0.37[a] | 1.20±0.21[a] | 1.59±0.46[ab] | 0.40±0.95[a] | 0.001** |
| hsCRP(mg/l) | 2.80±0.12[a] | 2.94±0.13[a] | 2.86±0.13[a] | 3.10±0.17[a] | 1.83±0.05[b] | 0.001** |
| Lipid profile and lipid ratios | | | | | | |
| Total cholesterol (mg/dl) | 165.10±4.09[a] | 170.23±4.28[a] | 173.26±4.04 [a] | 177.40±5.44[a] | 159.77±2.98[ab] | 0.382 |
| Triglyceride (mg/dl) | 122.01±4.90[a] | 127.94±6.38[a] | 133.31±6.79[a] | 134.42±8.86[a] | 120.20±4.15[a] | 0.268 |
| HDL-C (mg/dl) | 40.19±1.17[a] | 39.65±1.39[a] | 38.86±1.22[a] | 31.81±1.69 [a] | 40.45±0.88 [a] | 0.894 |
| LDL-C (mg/dl) | 65.37±3.98[a] | 67.60±5.11[a] | 69.16±5.1[a] | 90.57±5.30 [b] | 58.74±3.56[a] | 0.001** |
| Non-HDL (mg/dl) | 124.91±4.44[a] | 130.58±4.84[a] | 134.4±4.00[a] | 145.59±5.67[a] | 119.32±3.36[a] | 0.479 |
| Total cholesterol /HDL ratio | 4.13±0.15[a] | 4.34±0.19[a] | 4.48±0.13[b] | 5.59±0.22[a] | 3.50±0.12[a] | 0.001** |
| LDL/HDL ratio | 1.63±0.12[a] | 1.75±0.17[a] | 1.78±0.15[a] | 2.84±0.21[a] | 1.51±0.99[a] | 0.671 |
| Hematological index | | | | | | |
| Leukocyte count ($10^3$/µL) | 6.90±0.17[a] | 7.08±0.25[a] | 7.36±0.22[a] | 7.44±0.35[a] | 6.79±0.10[ab] | 0.153 |

Values are expressed as mean ± SE, tests among groups (ANOVA), various letters mean significant differences among the groups ($p<0.05$), and similar letters mean no significant differences ($p>0.05$).

Non-DM-Non-HTN, non-diabetic non-hypertensive, DM, diabetes, HTN, hypertensive, DM-HTN, diabetic hypertensive

Non-DM, Non-HTN denoted 30 percent of patients, followed by DM-HTN, HTN, and DM (26%, 24%, and 20%, respectively). In group DM-HTN, the mean value of BMI, age, triglycerides, LDL-C, total cholesterol/HDL, and LDL /HDL was higher with significant total cholesterol. Table 2 provides the details.

Patients ≥55 were discovered in more significant numbers in the DM-HTN group (84.61 percent) than in the other groups. The group DM-HTN had the highest rate of smokers (57.69), followed by the non-DM-non-HTN group (26.66 percent ). The mean duration of DM and HTN was higher in the DM-HTN group compared to the DM-HTN group, and HTN was higher in the DM-HTN group compared to the DM-HTN group ($p>0.05$). RCA was the least often impacted artery in the patient group, whereas HTN was the least affected by three diseased vessels in the patient group (Table 3).

Pearson's correlation coefficient revealed a strong positive association between sCD36 and hs-CRP ($r=0.319$, $p=0.001$) ($p<0.05$). The same above result were reported between sCD36 and BMI ($r=0.546$, $p=0.001$), total cholesterol ($r=0.212$, $p=0.048$) and non-HDL ($r=0.238$, $p=0.025$) ($p<0.05$). Negative non-significant correlation was reported between HDL as protective biomarker and both inflammatory biomarkers (sCD36 and hs-CRP). Inverse correlation

result was observed comparing LDL with inflammatory biomarkers (sCD36 and hs-CRP) (Table 4).

**Table 3.** Comparison of some risk factors and other variables in coronary atherosclerosis patient and control groups

| Variables | Patient groups | | | | Control | Statistical analysis |
|---|---|---|---|---|---|---|
| | Non-DM Non-HTN n 30 (30%) | DM only n 20 (20%) | HTN only n 24 (24%) | DM-HTN n 26 (26%) | Non-DM Non-HTN n 59 (59%) | P-Value |
| Age (years) ≥ 55 | 20 (66.66) | 18 (90) | 21 (84.61) | 22 (84.61) | 5 (8.47) | 0.058 |
| Male (%) | 25 (83.33) | 14 (70) | 14 (58.33) | 9 (34.61) | 1 (1.69) | 1.000 |
| Smoker (%) | 8 (26.66) | 6 (30) | 6 (25) | 15 (57.69) | 1 (1.69) | 0.417 |
| Duration of diabetes mellitus (years) * | - | 8.60±1.93 | - | 8.50±2.46 | - | 1.000 |
| Duration of hypertension (years) * | - | - | 6.14±1.80 | 3.60±1.14 | - | 0.249 |
| Numbers of affected vessels | | | | | | |
| 1 vessel (%) | 14 (46.66) | 9 (45) | 15 (62.4) | 14 (43.84) | - | 0.001** |
| 2 vessels (%) | 8 (26.66) | 3 (15) | 4 (16.66) | 3 (11.53) | - | |
| 3 vessels (%) | 8 (26.66) | 8 (40) | 5 (20.83) | 9 (34.61) | - | |
| Location of the Culprit lesion | | | | | | |
| LAD (%) | 12 (40) | 15 (80) | 10 (41.66) | 13 (50) | - | 0.001** |
| RCA (%) | 7 (3.33) | 2 (10) | 4 (33.33) | 4 (23.07) | - | |
| LCX (%) | 11(36.66) | 3 (15) | 10 (41.66) | 9 (34.61) | - | |
| Medication | | | | | | |
| Statin (%) | 3 (10) | 11 (55) | 4 (16.66) | 4 (15.38) | - | 0.238 |

Significance tests between groups (chi-square and Fisher exact tests), t-test analysis*. Values are expressed as mean ± SE, Non-DM-Non-HTN, non-diabetic non-hypertensive, DM, diabetes, HTN, hypertensive, DM-HTN, diabetic hypertensive.

**Table 4.** Correlation of sCD36 with different risk factors in coronary atherosclerosis patients

| Parameters | sCD36 | | hs-CRP | |
|---|---|---|---|---|
| | r | P-value | r | P-value |
| Age | 0.027 | 0.801 | 0.059 | 0.557 |
| BMI | 0.546 | 0.001** | 0.070 | 0.489 |
| sCD36 | - | - | 0.319 | 0.001** |
| Total cholesterol | 0.212 | 0.048* | -0.015 | 0.884 |
| Triglyceride | -0.007 | 0.951 | 0.057 | 0.573 |
| HDL-C | -0.149 | 0.166 | -0.117 | 0.246 |
| LDL-C | 0.128 | 0.235 | 0.026 | 0.800 |
| Non-HDL | 0.238 | 0.025* | 0.019 | 0.849 |
| Leukocytes | 0.041 | 0.703 | 0.821 | 0.416 |

r: Pearson correlation, P: P-value,
*P<0.05: Significant, **P<0.01: Highly significant, p>0.05: Non-significant.

The present research was designed to study the relationship of soluble CD36 with cardiovascular risk factors among atherosclerotic cases in the Kurdistan region-Iraq. The current study shows an increased significant difference in circulating sCD36 concentrations between patients and controls and a significant positive association between sCD36 and hs-CRP. This finding agrees with those of Handberg et al. (8) in Denmark and other studies (18,19), demonstrating that sCD36 is higher in the patient groups than the control group.

Himoto et al., (20) and García-Monzón et al., (21) found lower sCD36 concentrations in comparison to this research. Furthermore, specific parameters such as lipid consumption (22) and blood glucose level can influence cellular CD36 expression (23). Nevertheless, the lack of a generally reliable standardized method for assessing circulating sCD36 may be another reason for inconsistency in sCD36 concentrations (24), and this debate could reflect race variation between different populations. In this study, the DM-HTN group had a significant rise in both sCD36 and hs-CRP compared to other patient groups. Few investigations compare sCD36 with hs-CRP in diabetic hypertensive patients with coronary atherosclerosis to the best of the researcher's knowledge. This result is compatible with the present study. Our result is consistent with prior research (18,25), where the observation group has a sensationally higher CRP level than the control group in coronary atherosclerosis. Tissue necrosis is an effective acute phase inducer. The CRP, a non-specific circulatory acute phase reactant, showed a significant response, and its level reflects the magnitude of myocardial necrosis. In coronary atherosclerosis, there is local and systemic cellular and humoral inflammatory reaction which aims to recruit the process of healing and scar formation, there is an increase in circulatory CRP level following the cytokine activation, and it binds to the cell membrane of dead cells, assisting in the complement activation and thus encouraging more inflammatory reactions, injury of cardiomyocytes, and extension of necrosis (26). Although all parameters were higher in the DM-HTN group, HbA1c and LDL levels were significant risk factors for atherosclerosis, indicating that DM and HTN cases experienced more complicated states. A previous study suggests that the degree of coronary artery stenosis is positively related to total cholesterol levels in the blood but negatively related to HDL-C levels (18). Increased level of HbA1C is probably due to persistent insulin resistance since there is a clear association between insulin resistance and metabolic disturbances such as hyperglycaemia, dyslipidaemia, and inflammation; this might be considered an essential pathological mechanism for the adverse effect of increased HbA1C in CAD patients (27). It has been observed that oxidized LDL activates macrophages and T cells, stimulates adhesion molecules expression, triggers macrophages to sarcoplasmic reticulum and induces foam cells production. Oxidizing LDL with its contained cholesterol plays a significant role in plaque formation, which starts with the damage caused by a combination of unsaturated fats of arterial membrane or plasma with oxygen or with side products produced from their oxidation (28). The above explanation is compatible with our correlation result in which a positive correlation was reposted between LDL-C and inflammatory biomarkers (sCD36 and hs-CRP). As a result, our research confirms the findings of earlier studies while having several distinct strengths and limitations. Clinically, our research has the advantage of introducing a new biomarker, sCD36, in a population-based prospective scenario. Nevertheless, because sCD36 is involved in cholesterol accumulation in the artery wall, it has the potential to be a combined risk marker of HTN and its related atherosclerosis risk. So sCD36 has the potential to have a significant impact in terms of screening and prevention. To begin, ample prospective research is required to determine the utility of sCD36 blood levels as a predictor of cardiovascular disease. Second, we controlled for risk factors found to be correlated with atherosclerosis; nonetheless, the chance that some other confounding factors could have been overlooked remains. Third, if sCD36 were to be employed as a biomarker, it would be preferable to detect it using a standardized ELISA conducted in any basic laboratory rather than the specialized flow cytometry procedures necessary to count microparticles.

## Conclusion

In conclusion, comparing inflammatory biomarkers of sCD36 and hs-CRP in atherosclerosis patients, the sCD36 could be used as a more dependable predictor to assess the intensity of the disease complicated with DM-HTN.

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None

## Interest conflict

The authors declare no conflict of interest.

## Author's contribution

Amer Ali Khaleel: Writing, data analysis Ruqaya Mohammed Ghareeb Taher Al-Barzinji: Supervision

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