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Original Research

Indian Patients with Type 2 Diabetes Mellitus: Looking For Potential Biomarkers to Detect Atherosclerosis

Dr. Manish Kumar Singh[1], Dr. Yogesh Kumar Mishra [2], Dr. Pankaj Mehrotra [3], Dr. Ravindra Mohan Katiyar [4]

[1]Associate Professor, Department of General Medicine, Rama Medical College- Hospital & Research Centre, Kanpur, U.P., India
[2]Assistant Professor, Department of General Medicine, Rama Medical College, Hospital & Research Centre, Kanpur, , U.P., India
[3]Associate Professor, Department of General Surgery, Rama Medical College- Hospital & Research Centre, Kanpur , U.P., India
[4]Assosiate Professor, Department of General Medicine, Rama Medical College, Hospital & Research Centre, Kanpur, , U.P., India

Corresponding Author:
Dr. Yogesh Kumar Mishra
Assistant Professor, Department of General Medicine, Rama Medical College-Hospital & Research Centre, Kanpur

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ABSTRACT

Background & Objectives: A range of biological markers indicative of subclinical atherosclerosis have been suggested as predictors of cardiovascular events in individuals with diabetes mellitus. Nevertheless, there exists a limited number of clinical studies evaluating the role of invasive biomarkers [CD-36, peroxisome proliferator-activated receptor gamma (PPAR-γ), and YKL-40] in Indian patients diagnosed with type 2 diabetes mellitus (T2DM). Consequently, the current study was undertaken to evaluate the protein levels and gene expression of CD-36, PPAR-γ, and YKL-40 in individuals diagnosed with Type 2 Diabetes Mellitus (T2DM) and to compare these parameters with those observed in hypertensive and healthy control groups.

Material & Methods: All participants underwent assessment of their medical histories, anthropometric measurements, and evaluations of biochemical and biomarker levels utilizing both enzyme-linked immunosorbent assay (ELISA) and real-time polymerase chain reaction methodologies. The study cohorts included patients diagnosed with Type 2 Diabetes Mellitus (T2DM) for a duration exceeding five years and concurrently presenting with hypertension (n=55), as well as patients diagnosed solely with T2DM (<2yr) without hypertension (n=28 yr), hypertensive controls (n=31) and healthy controls (n=30).

Results: The expression levels of the genes YKL-40 and CD36 were markedly elevated in individuals diagnosed with type 2 diabetes mellitus of over five years' duration and concurrent hypertension when compared to a cohort of healthy controls (P=0. 006). Furthermore, a considerable elevation in serum levels of CD36, PPAR-γ, and YKL-40 was noted in patients with Type 2 Diabetes Mellitus (T2DM) of more than five years duration, who also have hypertension, when compared to healthy control subjects (P).

Interpretation & Conclusions: CD36 and YKL-40 are potential inflammatory biomarkers indicative of the early onset of atherosclerosis in individuals diagnosed with Type 2 Diabetes Mellitus (T2DM).

Key Words CD36, peroxisome proliferator, activated receptor gamma, Type 2 diabetes mellitus, YKL40.

INTRODUCTION

Diabetes mellitus (DM) constitutes a global public health concern impacting individuals across all age groups. It is approaching the threshold of a pandemic within India, with over 72 million documented cases in the year 2017.[1] The autoimmune destruction of β-cells leads to the development of Type 1 Diabetes Mellitus (T1DM), whereas conditions that diminish insulin sensitivity and negatively impact β-cell function result in Type 2 Diabetes Mellitus (T2DM).[2]

Diabetes Mellitus (DM) is closely linked to both microvascular complications, including retinopathy, nephropathy, and neuropathy, as well as macrovascular complications such as coronary artery disease (CAD), peripheral arterial disease, and stroke. These associations often lead to organ and tissue damage in

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approximately one-third to one-half of affected individuals.[3] Atherosclerosis constitutes the primary pathological process in macrovascular disease, resulting in the constriction of arterial walls. Empirical evidence substantiates the pivotal role of the endothelium and inflammatory mechanisms throughout all phases of the atherosclerotic process.[4] Individuals with Type 2 Diabetes Mellitus (T2DM) exhibit insulin resistance, leading to manifestations such as hyperglycemia, dyslipidemia, hypertension, and coagulopathy. These pathological states serve as catalysts for the premature development of atherosclerosis.[5] Potential biomarkers, including CD36 and peroxisome proliferator-activated receptor gamma (PPAR-γ), Furthermore, YKL-40 may play significant roles in the development of insulin resistance and atherosclerosis in individuals diagnosed with Type 2 Diabetes Mellitus (T2DM). CD36 is a multi-ligand scavenger receptor located on the surface of monocytes and macrophages. It establishes a connection and Engages in the endocytosis of oxidized low-density lipoprotein (LDL) and is implicated in the formationof foam cells. Therefore, CD36 is integral to the pathogenesis of atherosclerotic lesions[6]. The articulation of scavenger The expression of receptor CD36 is augmented in the presence of PPAR-γ.[7] The expression levels of both PPAR-γ protein and mRNA are substantially elevated in patients diagnosed with coronary artery disease (CAD) when compared to healthy individuals, with the former presenting approximately a tenfold increase and the latter exhibiting approximately a sixtyfold augmentation.[8] This phenomenon has been extensively documented in the literature. YKL-40 is a newly identified biomarker that is expressed. and is secreted by macrophages. The expression of YKL-40 mRNA is significantly elevated in macrophages, particularly in those that infiltrate more profoundly into the atherosclerotic lesion.[9] Numerous biological markers have been proposed as potential predictors of cardiovascular events in patients. utilizing direct messaging. A comprehensive understanding of these biomarkers is crucial in elucidating the biological mechanisms of cytokines and endothelial dysfunction in the development of insulin resistance. Consequently, this study was conducted to assess the significance of these potential biomarkers in detecting subclinical atherosclerosis among patients with Type 2 Diabetes Mellitus (T2DM), both with and without hypertension, and to compare findings against hypertensive control subjects as well as healthy control subjects.

MATERIAL & METHODS

The investigation comprised subjects who had been diagnosed with Type 2 Diabetes Mellitus (T2DM) for a duration exceeding five years and who also had concurrent hypertension (Group A-I, n=100). Additionally, it included newly diagnosed T2DM patients without hypertension (Group A-II, n=54), individuals with primary hypertension only (hypertensive controls; Group B-I, n=52), and a cohort of healthy controls (Group B-II, n=48). Participants were systematically selected over a duration of one year and five months, spanning from November 2011 to April 2013, from the Diabetes Clinic located at Sir HN Hospital in Mumbai, India. Individuals with notable systemic illnesses (excluding diabetes mellitus and hypertension for Groups A-I, A-II, and B-I), as well as those diagnosed with autoimmune or chronic inflammatory conditions, individuals taking thiazolidinediones (PPAR-γ agonists) and direct vasodilators, and women who are pregnant or lactating were excluded from the study. The determination of health status in the control group was based on a comprehensive assessment, including a review of medical history, a physical examination, and a series of laboratory investigations. All participants were aged above 40 years and comprised individuals of both genders, who were recruited from the hospital personnel. This study was designed to generate hypotheses regarding the role of various biomarkers and their associated genes within the Indian population. Therefore, a formal sample size calculation was not conducted. Nonetheless, considering the extant literature pertaining to these genes, a sample size of 30 individuals per group was determined to be adequate for yielding a statistically significant association between Type 2 Diabetes Mellitus (T2DM) and various biomarkers. A decision was made to enroll participants in a ratio of 2:1:1:1 for this study.

The Institutional Ethics Committee granted approval for the study. Informed consent in written form was procured from all of the participants. Demographic data, in conjunction with personal and familial medical histories, as well as records of smoking, alcohol, or substance abuse, were systematically documented. Anthropometric parameters, specifically height (in centimeters), weight (in kilograms), body mass index (BMI), and waist-to-hip ratio, were systematically evaluated. Two measurements of blood pressure, systolic and diastolic, were obtained using a mercury sphygmomanometer, and the mean value of these measurements was employed for analytical purposes. All the investigations were performed after overnight fasting. Five millilitres of blood was collected from each participant in ethylene di-amine tetra acetic acid (EDTA) and plain bulb. After centrifugation, serum sample was used for estimation of fasting blood sugar and lipid profile (Konelab® prime 30 automatic analyzer, Thermo Fisher Scientific, USA). EDTA sample was used for analyzing glycosylated haemoglobin. Postprandial blood sugar was measured at two hours post-lunch. All laboratory analyses were

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conducted within a two-hour timeframe following the collection of samples. Serum levels of YKL-40, PPAR-γ, and soluble CD36 were quantitatively assessed utilizing a commercially available assay kit. Conduct an assay on the serum sample preserved at a temperature of −80°C. The analysis of YKL-40 was conducted utilizing Human Chitinase 3-like 1. The Quantikine ELISA Kit, produced by RandD Systems located at 614 McKinley Place NE, Minneapolis, USA, possesses a measurement range of 15. 9 to 93. 5 ng/ml and a coefficient of variation (CV) <5%]. Diego, USA (range, 2-600 ng/ml; CV <10%) and CD36 was analyzed by Human Soluble Cluster of Differentiation 36 (sCD36) ELISA kit by MyBioSource, San Diego, USA (range, 2-110 ng/ml; CV <10%). The gene expressions of the biomarkers, namely CD36, PPAR-γ, and YKL-40, were Conducted research on monocytes. A methodology, as developed by Graziani-Bowering et al. [10], was employed to separate. Monocytes can be differentiated from lymphocytes based on their flotation rate within leukocyte-rich plasma. The aforementioned method provided monocytes of high purity and viability. Cytoplasmic RNA (NucleoSpin, Macherey-Nagel, A sample from Germany was prepared, and the synthesis of the first-strand complementary DNA (cDNA) was carried out using the High Capacity® Reverse Transcription kit from Applied Biosystems, USA, in accordance with the instructions provided by the manufacturer. The real-time polymerase chain reaction was conducted utilizing the Step One Plus system from Applied Biosystems, located in Foster City, California, USA. This procedure employed the TaqMan® Gene Expression Assay, also from Foster City, California, USA, along with specific primers and probes targeting PPAR-γ, CD36, YKL-40, and β-Actin. The calculation of relative gene expression was conducted utilizing the $2^{-\Delta\Delta CT}$ method [11]. The data are presented as the fold change in the expression of the target. The gene in relation to the internal control gene (β-Actin). The normality of the numerical data was assessed utilizing the Kolmogorov-Smirnov test, and A comparison between groups was conducted utilizing a one-way analysis of variance, followed by a post hoc unpaired test. In instances where the data is normally distributed, a t-test should be employed. Conversely, if the data does not follow a normal distribution, the Kruskal-Wallis test is appropriate, followed by a post hoc Mann-Whitney U-test. distributed). Categorical data were analyzed employing the Chi-square test, Relationship between two quantitative variables, the evaluation of the variables, which did not exhibit a normal distribution, was conducted utilizing Spearman's rho correlation coefficient. The analyses were conducted utilizing SPSS software, version 21.0 (SPSS, Chicago, IL, USA).

RESULT

A total of 254 subjects participated in this research. Table I indicates that there were no significant variations in the anthropometric measurements distribution and demographic details, with the exception of blood pressure, among the four study groups. Systolic blood pressure was significantly higher in patients with T2DM (>10 yr) who had hypertension when compared to patients with T2DM (10 yr) who had hypertension when compared to patients with T2DM (<5 yr) without hypertension (P=0.01). Individuals diagnosed with hypertension were administered treatment involving one or more of the following pharmacological classes: angiotensin-II receptor antagonists, angiotensin converting enzyme (ACE) inhibitors, cardioselective beta-blockers and calcium channel blockers. Patients diagnosed with Type 2 Diabetes Mellitus (T2DM) were administered either combination or monotherapy therapy, comprising the following classes of antidiabetic medications: alpha-glucosidase inhibitors, biguanides, dipeptidyl peptidase IV (DPP-4) inhibitors, and sulfonylureas. Biochemical indicators, including fasting and postprandial blood glucose levels, as well as glycated hemoglobin (HbA1c), were found to be significantly elevated in patients with Type 2 Diabetes Mellitus (T2DM) when compared to both healthy control groups and hypertensive (both P=0. 006). A substantial decrease in serum LDL-cholesterol levels was observed in patients with type 2 diabetes mellitus (duration exceeding 10 years) who also have hypertension, as well as in hypertensive controls, when compared to healthy control subjects.

Serum Biomarkers: The serum concentrations of soluble CD36, PPAR-γ and YKL-40 were significantly elevated (P<0. 05) in subjects with a history of over ten years duration of type 2 diabetes mellitus (T2DM) concurrent with hypertension, as compared to both hypertensive and healthy control groups. Serum concentrations of CD36, YKL-40, and PPAR-γ exhibited significant elevation in individuals diagnosed with Type 2 Diabetes Mellitus (T2DM) as mention in Table No.2.

Gene expression of biomarkers: The expression levels of the CD36 and YKL-40 genes were significantly elevated in patients diagnosed with Type 2 Diabetes Mellitus for a duration exceeding ten years, who also presented with hypertension, in comparison to the healthy control group, as detailed in Table 3.

Correlation: Significant correlation was noted between the expression of CD36 and PPAR-γ genes (ρ=0.51, P<0.001). Serum levels of CD36 also observed

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significant correlation with serum levels of PPAR-γ (ρ=0.45, P<0.001).

A significant correlation was recorded between gene expression of YKL-40 and serum levels (ρ=0.48, P<0.001). Nevertheless, no statistically significant correlation was observed between serum levels and the gene expression of either CD36 or PPAR-γ. No statistically significant correlation was observed between HbA1c and the serum concentrations of CD36, YKL-40, or PPAR-γ.

Table No.1: Baseline characteristics of four study groups

Parameter	Group A-1 (n=100)	Group A-2 (n=54)	Group B-1 (n=52)	Group B-2 (n=48)	P
Age (year)	58.4±8.5	53.3±9.6	56.4±9.4	52.1±8.9	0.1
Gender ratio (M:F)	58:42	28:26	30:22	27:21	0.89
Duration (year)					
T2DM	13 (8-22)	11 (6-20)	-	-	
HT	15 (7-21)	-	13 (7-21)	-	
BMI (Kg/m^2)	27.2±6.4	25.1 (4.3)	27.3±5.1	26.3±5.3	0.38
Waist to hip ratio	0.9±0.5	0.8±0.7	0.9±0.6	0.8±0.4	0.1
Systolic BP	146±17	135±16	137±18	130±12	0.001
Diastolic BP(mmHg)	81±8	79±5	83±6	78±4	0.01
Glucose profile					
Fasting blood Glucose (mg/dl)	150.2±48.5	148.5±58.5	104.4±25.9	101.3±23.6	0.001
Postprandial blood glucose (mg/dl)	218.7±64.8	179.6±81.2	121.6±45.4	106.5±25.4	0.001
HbA1c (%)	7.8±1.32	6.31±1.46	5.0±0.7	5.06±0.5	0.001
Lipid profile (mg/dl)					
Total cholesterol	172.4±58.3	196.8±54.9	162.3±46.3	182.4±44.2	0.02
HDL cholesterol	48.1±14.1	54.3±16.3	51.4±24.2	49.1±12.52	0.3
LDL cholesterol	94.8±48.6	112.4±33.4	88.5±31.1	117.4±26.8	0.001
Triglycerides	144.2±81.4	137.2±55.2	108.5±42.3	107.3±48.3	0.01
Antidiabetic therapy, n (%)					
SU	21 (21)	12 (22.2)	NA	NA	NA
SU + biguanides	41 (41)	20 (37.0)			
SU + biguanides + dipeptidyl Peptidase 4 inhibitors	29 (29)	15 (27.8)			
Biguanides + α-glucosidase inhibitors	9 (9)	7 (12.9)			
Antihypertensive therapy, n (%)					
ACE inhibitors	32	NA	12 (23.1)	NA	NA
ARBs	29	NA	11 (21.1)	NA	
ARB + calcium channel blockers	39	NA	23 (44.2)	NA	
Metoprolol	0	NA	6 (11.5)	NA	

Values are provided as mean±Standard Deviation, ACE- angiotensin-converting enzyme; ARBs- angiotensin-II receptor blockers; T2DM- type 2 diabetes mellitus; HT- hypertension; BMI- body mass index; HbA1c- glycated haemoglobin; HDL- high-density lipoprotein; LDL- low density lipoprotein; SU- sulphonylureas; NA- not available

Table No. 2: Serum levels of biomarkers involved in vascular dysfunction measured by ELISA in the study groups

Biomarkers	Group A-1 (n=100)	Group A-2(n=54)	Group B-1(n=52)	Group B-2(n=48)	P
sCD36 (ng/ml)	44.16±9.61	38.82±7.97	28.3±9.1	27.2±10.2	<0.001
PPAR-γ (ng/ml)	107.6±45.21	76.4±14.1	75.1±7.4	67.3±12.9	<0.001
YKL-40 (ng/ml)	148.6±39.2	112.3±34.9	44.5±8.1	29.6±15.1	0.02

Values given as mean±Standard Deviation. PPAR-γ- peroxisome proliferator-activated receptor gamma; sCD36-

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soluble cluster of differentiation 36.

Table No. 3: Gene expressions across the study groups

Biomarkers	Group A-1 (n=100)	Group A-2 (n=54)	Group B-1 (n=52)	Group B-2 (n=48)	P
CD36	1.21±0.18	0.92±5.1	0.94±0.70	0.97±0.72	0.05
PPAR-γ	1.55±0.21	0.94±0.61	1.16±0.23	1.21±0.72	0.3
YKL-40	4.28±0.46	3.31±0.16	4.15±1.65	0.83±0.89	0.001

Values given as mean±Standard Deviation. PPAR-γ- peroxisome proliferator-activated receptor gamma; sCD36- soluble cluster of differentiation 36.

DISCUSSION

The findings of the current study indicate that the serum protein levels of CD36, YKL-40, and PPAR-γ were markedly elevated in individuals with Type 2 Diabetes Mellitus (T2DM) relative to the healthy control group. The expression levels of the genes YKL-40 and CD36 were found to be significantly elevated in patients suffering from Type 2 Diabetes Mellitus (with a duration of greater than five years) when compared to healthy control subjects. A significant correlation was observed between serum levels and gene expression of CD36 with those of PPAR-γ, respectively. A statistically significant moderate correlation was identified between serum concentrations and gene expression levels of YKL-40. CD36 engages in the binding and internalization of modified low-density lipoprotein (LDL), thereby facilitating the formation of macrophage foam cells laden with lipids. It is posited to exert a crucial influence in the onset and advancement of atherosclerosis[12]. Consequently, CD36 has been associated with conditions pertaining to metabolic dysregulation, encompassing obesity, insulin resistance, diabetes mellitus, diabetic nephropathy, and atherosclerosis[13]. This may elucidate the concomitant acceleration of CD36 expression with the advancement of atherosclerosis. The present study demonstrated elevated serum sCD36 concentrations in individuals with Type 2 Diabetes Mellitus (T2DM) relative to healthy control subjects, corroborating the findings of Handberg et al[14]. and Alkhatatbeh et al[15]. The expression of CD36 mRNA in monocytes was observed to be significantly elevated in patients with Type 2 Diabetes Mellitus exceeding five years in duration, in comparison to both hypertensive individuals and healthy control subjects. This observation is consistent with the findings of Han et al[16]. , who reported a concordance between the expression of CD36 mRNA and increased levels of CD36 protein in serum. Research has established that the expression of CD36 on monocytes is upregulated in the presence of oxidized low-density lipoprotein (ox-LDL), the levels of which are elevated in instances of Type 2 Diabetes Mellitus (T2DM) and associated atherosclerosis. Soluble CD36 serves as an indicator of plaque instability and symptomatic carotid atherosclerosis, potentially due to the release of CD36 into the circulation from foam cells residing within the atherosclerotic lesion[17]. A separate study has demonstrated an upregulation in CD36 transcript levels under conditions of elevated glucose concentrations, thereby offering a potential mechanistic explanation for the accelerated development of atherosclerosis observed in patients with diabetes mellitus[18]. This indicates that individuals diagnosed with Type 2 Diabetes Mellitus (T2DM) who exhibit elevated levels of soluble CD36 (sCD36) may experience an earlier onset of subclinical atherosclerosis. PPAR-γ ligands exert significant influence on all vascular cells pertinent to the pathogenesis of atherosclerosis, including vascular smooth muscle cells, endothelial cells (ECs), and monocytes/macrophages[19]. Peroxisome proliferator-activated receptor gamma (PPAR-γ) modulates a diverse array of cellular processes that influence glucose homeostasis, endothelial function, and inflammatory responses within the vessel wall. Furthermore, it enhances the expression of CD36. The findings of our study were consistent with the established role of PPAR-γ. PPAR-γ agonists are advantageous for individuals diagnosed with Type 2 Diabetes Mellitus (T2DM) due to their ability to reduce hepatic glucose production and extend the functionality of pancreatic β-cells by inhibiting the apoptotic processes in these cells[20]. The serum concentrations of PPAR-γ were observed to be notably elevated in patients with Type 2 Diabetes Mellitus (T2DM) of more than five years duration compared to other cohorts in the study. Within the context of the present study, the gene expression of PPAR-γ did not exhibit any statistically significant differences across the groups under investigation. The results of this study are consistent with the findings reported by Teupser et al [21]. YKL-40 is implicated in endothelial dysfunction among individuals with type 2 diabetes mellitus [22]. In vitro investigations have demonstrated that YKL-40 facilitates chemotaxis, cell attachment, spreading, and migration of vascular endothelial cells (ECs), indicating a potential involvement of YKL-40 in the formation of atherosclerotic plaques. Elevated expression of YKL-40

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mRNA was observed in macrophages infiltrating more deeply into atherosclerotic lesions, whereas the maximal expression levels of YKL-40 protein were detected in macrophages located within the early stages of atherosclerotic lesions [23].In the current study, both serum levels and gene expression of YKL-40 exhibited a significant increase in patients with Type 2 Diabetes Mellitus (T2DM) of over ten years' duration accompanied by hypertension, when compared to healthy control subjects. Nielsen et al. discovered that individuals with Type 2 Diabetes Mellitus (T2DM) exhibited elevated plasma levels of YKL-40 in comparison to healthy control subjects [24]. It has been proposed that YKL-40 may play a role in glucose metabolism. Michelsen et al [25]. have identified YKL-40 as a potential marker of plaque instability, possibly indicative of macrophage activation and matrix degradation within the atherosclerotic lesion. The study conducted by Kastrup and colleagues has illustrated that circulating levels of YKL-40 may serve as an indicator of the overall burden of coronary atherosclerosis or may assist in identifying high-risk phenotypes of atherosclerosis [26]. Røndbjerg et al [27]. have additionally posited a potential involvement of YKL-40 in the advancement of vascular complications among individuals diagnosed with Type 2 Diabetes Mellitus (T2DM). Elevated concentrations of YKL-40 have been identified as being correlated with both all-cause and cardiovascular mortality in individuals diagnosed with stable coronary artery disease (CAD). Consequently, elevated levels of YKL-40 in patients with long-standing type 2 diabetes mellitus may serve as an indicator for the early detection of atherosclerosis in this population. A significant correlation was exclusively observed between serum levels and gene expression for YKL-40; no such correlation was identified for CD36 or PPAR-γ. The disparity observed between gene expression and serum levels may result from non-monocyte gene expression, variations in monocyte secretion among different patient cohorts, and differences in the clearance rates of serum biomarkers. The constraints of the present study are attributed to its cross-sectional design, precluding any long-term follow-up of the patients. Consequently, this limitation impedes the assessment of the risk associated with developing cardiovascular events across the various study groups. The sections of the current study addressing non-invasive biomarkers[28] and examining the impact of small, dense low-density lipoprotein cholesterol (sd LDL-C) on cardiovascular risk among patients with type 2 diabetes mellitus (T2DM) have been previously published [29].

CONCLUSION

Inflammatory biomarkers, including CD36 and YKL-40, have considerable significance in atherogenic processes, encompassing foam cell formation, plaque instability, and the release of inflammatory mediators. Evaluation of these biomarkers in individuals with Type 2 Diabetes Mellitus (T2DM) may facilitate a deeper understanding of the pathogenic mechanisms that contribute to the development of cardiovascular diseases. Future investigations should prioritize the validation of CD36 and YKL-40 within diverse and extensive populations diagnosed with Type 2 Diabetes Mellitus, inclusive of individuals exhibiting insulin resistance.

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