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Association between high-sensitivity C-reactive protein and lipid profile in patients with type 2 diabetes mellitus

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Abstract---Background: The most significant and challenging health issue of the modern era is diabetes mellitus and its complications. Inflammation plays a crucial role in the development and progression of diabetes. Type 2 Diabetes Mellitus patients(T2DM) are at significant risk of developing cardiovascular diseases. High-sensitive CRP (hs-CRP) has become a reliable indicator of low-grade inflammation. Since very little is known regarding the relationship between hs-CRP and T2DM, the goal of this study was to evaluate hs-CRP levels and lipid profile and to study their relationship to cardiovascular problems in Type 2 Diabetes Mellitus patients. Material and Methods: The current study was carried out at Index Medical College and Hospital in Indore. The study group consisted of 70 healthy controls and 70 Type 2 Diabetes Mellitus patients who had been diagnosed following WHO criteria. Serum hs-CRP concentrations as well as the lipid profile (total cholesterol, HDL, and TG) were assessed. SPSS version 26 was used to analyze the data. Results: In comparison to controls, individuals with Type 2 Diabetes Mellitus had significantly higher levels of hs-CRP, with a mean value of 2.49 + 1.15 mg/L ($p < 0.001$). Additionally, it was determined that cases with Type 2 diabetes mellitus had significantly higher serum total cholesterol, LDL, VLDL, and TG levels than controls ($p < 0.001$). Moreover, we found that 22 (31%) of the diabetic patients had serum hs-CRP levels >3 mg/L, with a high risk of developing CVD whereas 40 (57%) of them had an intermediate risk

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of developing CVD with serum hs-CRP values between 1-3 mg/L. Conclusion: The present study showed that patients with T2DM had considerably higher levels of hs-CRP and lipid parameters than the controls. Furthermore, it was indicated that in patients T2DM patients with higher hs-CRP levels >3 mg/L there was a significant association between BMI, serum LDL-C, total cholesterol, and triglycerides. These results imply that hs-CRP may serve as a helpful tool for assessing atherosclerosis risk and cardiovascular complications in T2DM patients.

Keywords---hs-CRP, lipid profile, type 2 diabetes mellitus, cardiovascular disease.

Introduction

A group of metabolic disorders known as diabetes characterised by hyperglycemia results from deficiencies in insulin secretion, action, or both[1]. According to the World Health Organization's most recent data from 2016, an estimated 422 million adults worldwide have diabetes mellitus. By the end of 2040, this figure is expected to rise to 642 million[2]. Due to its concurrent microvascular sequelae, including neuropathy, nephropathy, and retinopathy as well as macrovascular problems, such as cardiovascular illnesses resulting in myocardial infarction and stroke, chronic hyperglycemia is accompanied by a high mortality and morbidity rate [3,4].

The exact etiopathogenesis of diabetes is still up for debate, despite significant progress in understanding its etiology. Reactive oxygen species, immunological responses, and inflammatory factors have all emerged as the main pathogenic effects of diabetes. The role of low-grade inflammation in the etiology of type 2 diabetes has drawn more and more attention [5].The three primary pro-inflammatory cytokines—tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), and interleukin-6(IL-6)—can, however, be produced and released by adipose tissue[6]. These cytokines, which are atherosclerotic risk factors, encourage the release of acute-phase proteins. Several metabolic processes related to insulin resistance, comprising reactive oxygen species, lipoprotein lipase activity, and adipocyte function, involve pro-inflammatory cytokines and acute phase reactants[7]. C-reactive protein (CRP) is an acute-phase protein that is elevated in inflammatory disorders such as diabetes, cancer, and coronary heart disease as well as infections.

A particularly sensitive variant of CRP is called high sensitivity CRP (hs-CRP). It has become the "golden biomarker" for malignancies and even inflammatory diseases [6,8]. It is detected using highly sensitive assays, which are capable of detecting CRP levels with a sensitivity range of 0.01 mg/L to 10 mg/L. In the absence of noticeable inflammation, these assays can therefore detect even low-grade inflammation. High sensitivity CRP levels quickly increase to more than 10 mg/L in acute situations. According to the American Heart Association, it is known that high sensitivity CRP levels > 1 mg/L are linked to a low risk of cardiovascular disease, whereas levels 1-3 mg/L is linked to moderate risk and >

3 mg/L to high risk [9-11]. Cytokines also influence the liver, resulting in the typical dyslipidemia of type 2 diabetes mellitus[12]. The relationship between cardiovascular illnesses and hs-CRP has been examined in a number of research. On the other hand, very little research has been conducted to study the relationship between hs-CRP and T2DM-related cardiovascular problems. Therefore, the purpose of the current study was to evaluate hs-CRP levels and lipid profiles in patients with T2DMand to study their relationship to cardiovascular problems in Type 2 Diabetes Mellitus patients.

Material and Methods

This hospital-based observational and comparative study was conducted between January 2021 and January 2022. The study was conducted in the Department of Medicine, Index Medical College, Indore and included 70 T2DM patients and 70 age- and sex-matched healthy controls. The Biochemical investigations were carried out in the Department of Biochemistry, Index Medical College and Hospital.

Inclusion criteria

Patients diagnosed with Type 2 Diabetes Mellitus who were above 30 years but under 60 years of age and met the WHO criteria (Fasting plasma glucose levels equal to or greater than 126 mg/dl and HbA1c > 6.5 percent) were included in the study[13].

Exclusion criteria

Patients taking anti-inflammatory medicines that are known to lower CRP levels, statins, and thiazolidinediones (TZDs) were excluded from the study. The study also excluded individuals with heart disease, acute febrile illness, kidney, liver, and malignant disorders, chronic illnesses, symptomless infections, type 1 diabetes, gestational diabetes, alcoholics, pancreatitis, other endocrinal disorders, individuals receiving diuretic therapy, and individuals taking amino-glycosides[13]. The patient's informed consent was obtained.

Sample collection

After 12 hours of fasting venous blood sample of all the participants was taken from ante-cubital vein under aseptic conditions. The sample was dispensed in fluoride vials for analysis of plasma glucose levels, in EDTA vials for HbA1c, and plain vials for lipid profile and hs-CRP. After 1 hour, serum was separated by centrifugation at 3,000 rpm for 10 minutes. Plasma glucose levels were determined using the GOD-POD method [14], HbA1c was calculated using the High-Performance Liquid Chromatography technique [15], serum cholesterol was determined using the cholesterol oxidase peroxidase method [16], serum TGs were determined using the Glycerol oxidase-Trinder method[17], and high-density lipoprotein (HDL) levels were determined using modified polyethylene glycol precipitation method[18]. The Fridelwald equation was used to compute LDL [19] Immunoturbidometric analysis of serum hs-CRP was performed using a COBAS-501 fully automated analyzer of Roche Diagnostics [20],[21].

Statistical analysis

SPSS version 26.0 was used to evaluate the data outcomes. For the distribution of diabetes cases and controls by age and BMI, descriptive data (frequency and percentage) were obtained. For both the cases and the healthy controls, the mean and SD were calculated. Using an independent t-test, the mean values of continuous variables were compared. Significance was assessed at a 5% level of significance. The association between hs-CRP and various other factors was analysed using Pearson's correlation coefficient test. One-way Anova was used to compare the means of different groups of T2DM patients categorised on the basis of their hs-CRP levels as low, intermediate and high risks of cardiovascular disease. The interpretation of results was done on the following basis:

- p-value <0.05 – Significant (S)
- p-value <0.01- Highly significant (HS)
- p-value > 0.05 – Not significant (NS)

Results

Table 1
Distribution of Type II Diabetic Mellitus Patients According to Age

AGE GROUP(YEARS)	NUMBER OF CASES (N=70)	PERCENTAGE
30-40	12	17.1%
41-50	25	35.7%
51-60	33	47.1%

Table 2
Distribution of healthy controls according to age

AGE GROUP(YEARS)	NUMBER OF SUBJECTS (N=70)	PERCENTAGE
30-40	16	22.8%
41-50	27	38.5%
51-60	27	38.5%

Table 3
Distribution of the study population according to BMI

BMI	DIABETIC CASES		CONTROLS	
(kg/m^2)	N(70)	%	N(70)	%
Below 18	1	1.42	5	7.14
18-24.99	21	30	41	58.57
25-29.99	37	52.85	21	30
30 and above	11	15.71	3	4.28
Mean + SD	26.29 +3.25		23.71+3.72	

Table 3 shows that 41 (58.57%) of the controls and 21 (30%) of the patients both had normal BMIs. 37 cases (52.85%) were found to be overweight (BMI 25–29.99), compared to 21 controls (30%) who fall into this category. 11 (15.71%) of the diabetic patients were obese with a BMI of 30 or higher, compared to 3 (4.28%) controls.

Table 4
Comparison of glycemic parameters between type II diabetic mellitus patients and healthy controls

PARAMETERS	DIABETIC CASES (Mean + SD)	CONTROLS (Mean + SD)	p-Value
FPG(mg/dl)	174.74 + 45.54	83.77 + 10.1	<0.001
PP(mg/dl)	259.78 + 90.6	122.08 + 12.25	<0.001
HbA1c (%)	9.97 + 2.36	5.30 + 0.61	<0.001

FPG, PPBS and HbA1c levels in diabetes patients were substantially higher than in controls. .The difference was highly significant with p-value<0.001

Table 5
Comparison of lipid profile between type II diabetic mellitus patients and healthy controls

PARAMETERS	DIABETIC CASES (Mean + SD)	CONTROLS (Mean + SD)	p-Value
TOTAL CHOLESTEROL (mg/dl)	204.30 + 38.27	168.59 + 38.24	<.001
HDL (mg/dl)	45.35 + 8.28	47.80 + 9.91	0.058
LDL (mg/dl)	117.45 + 38.59	90.44 + 33.14	<.001
VLDL (mg/dl)	41.48 + 11.55	30.35 + 12.67	<.001
TG (mg/dl)	207.44 + 57.77	151.77 + 63.38	<.001

According to the above table, cases with Type 2 diabetes mellitus had considerably higher serum total cholesterol, LDL, VLDL, and TG levels as compared to controls.

Table 6
Comparison of hs-CRP between type II diabetic mellitus patients and healthy controls

PARAMETERS	DIABETIC CASES (Mean + SD)	CONTROLS (Mean + SD)	p-Value
hs-CRP(mg/L)	2.49 + 1.15	1.22+ 0.54	<0.001

The hs-CRP levels in patients with Type 2 Diabetes Mellitus are significantly higher than those in controls, with a mean value of 2.49 + 1.15 mg/L versus 1.22 + 0.54 mg/L (p< 0.001), according to the above-mentioned table.

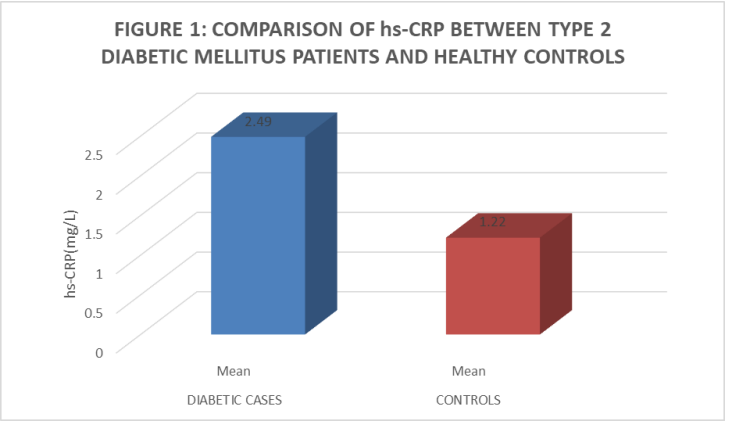
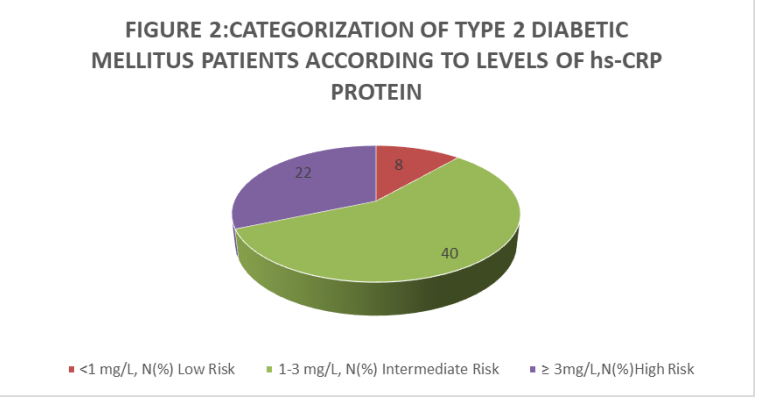


Table 7
Categorization of type 2 diabetic mellitus patients and healthy controls according to levels of hs-CRP protein

hs-CRP	DIABETIC CASES (n=70)	CONTROLS (n=70)
<1 mg/L, N(%) Low Risk	8	56
1-3 mg/L, N(%) Intermediate Risk	40	14
≥ 3mg/L,N(%)High Risk	22	0

In accordance with the above table, 8 (11.4%) of the 70 diabetes cases and 56 (49.5%) of the 70 controls have a low risk of developing cardiovascular disease (CVD), 40 (57.14%) of the cases and controls have an intermediate risk, and 22 (31.42%) of the cases have a high risk.



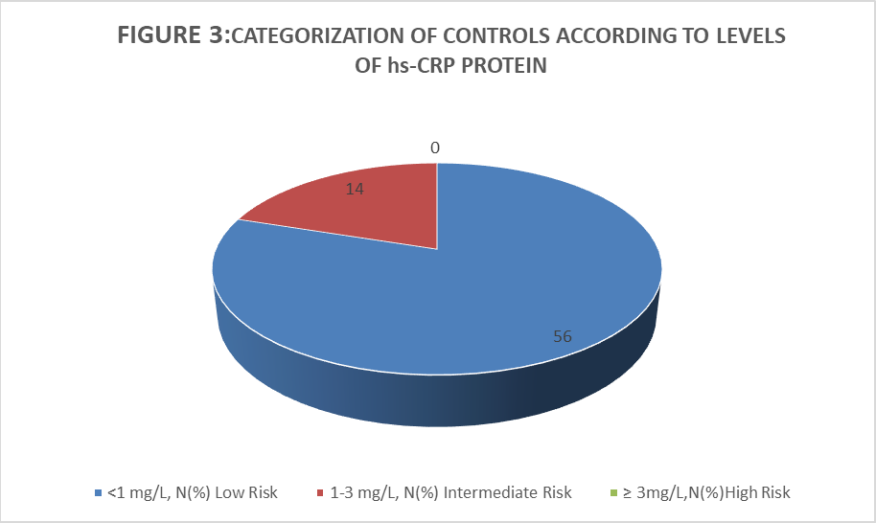


Table 8
Comparison of BMI and different parameters of lipid profile among three groups of hs-CRP

PARAMETERS	LOW RISK (Mean ± SD)	INTERMEDIATE RISK (Mean ± SD)	HIGH RISK (Mean ± SD)	p-value
BMI (kg/m^2)	23.01 ±3.44	25.59±2.59	28.63+2.85	0.005
TOTAL CHOLESTEROL (mg/dl)	160.75 ±27. 40	200.35±32.61	227.14±36.10	<0.001
HDL(mg/dl)	43.72 ±9.38	45.62±9.00	45.45±6.67	0.883
LDL(mg/dl)	87.22±33.05	116.74±38.62	129.58±35.60	0.023
VLDL(mg/dl)	29.80±5.72	37.98±8.39	52.10±10.18	<0.001
TG(mg/dl)	149.00±28.64	189.93±41.97	260.10±50.90	<0.001

According to Table 8, which elaborates the data for the BMI and lipid profile parameters in the three groups, it was observed that values of BMI, TC, LDL, and TG were considerably greater in patients with hs-CRP levels >3 mg/L than in those with hs-CRP levels 1-3 mg/L, which was higher than those with hs-CRP levels <1 mg/L.

Table 9
Distribution of patients with T2DM on the basis of their ldl levels in three groups of hs-CRP

	hs-CRP <1mg/L (N=8)	hs-CRP 1-3mg/L (N=40)	hs-CRP >3 mg/L(N=22)
LDL < 100mg/dl	7	15	3
LDL > 100mg/dl	1	25	19

The above table shows that 25(37.14 %) cases with Serum LDL levels >100mg/dl have their hs-CRP levels between the range of 1-3mg/L(Intermediate risk) whereas 19(27.14 %) of the cases have their hs-CRP levels >3 mg/L. 15(21.42%)out of 70 cases who have their LDL levels <100mg/dl ,their corresponding hs-CRP values were between 1-3mg/L, 7(10%) of the cases have their hs-CRP <1mg/L whereas 3(4.2%) have their hs-CRP levels above 3mg/L.

Discussion

The complex illness known as type 2 diabetes mellitus is due to diminished pancreatic function and decreased insulin action or resistance [22]. Type 2 diabetes, if unchecked, can result in long-term microvascular and macrovascular changes [23]. Nearly 80% of diabetes deaths are caused by vascular complications, including atherosclerosis [24]. Inflammation and insulin resistance have been linked in several studies to the pathophysiology of T2DM and the development of atherosclerotic plaques [25]. Reactive oxygen species, activated PKC, and activated glycation products are some of the potential pathways for the formation of atherosclerotic plaques. [26-28] . According to numerous research, inflammation causes an increase in hs-CRP levels, and hs-CRP concentration is related to future cardiovascular risk [28] .The pentameric protein known as hs-CRP, an inflammatory marker, is produced by hepatic cells under the influence of cytokines [29]. Previous research showed that high levels of serum hs-CRP are present in diabetes patients [30], which activates inflammatory pathways and advances CVD [31].

Therefore, the current study attempted to evaluate hs-CRP with glycemic parameters and lipid profile in patients with Type 2 Diabetes Mellitus. It also compared the levels of hs-CRP and lipid profile in patients with Type 2 Diabetes mellitus with that of healthy controls. We also investigated whether type 2 DM patients' hs-CRP levels are related to CVDs[32]. The distribution of Type 2 Diabetes Mellitus patients by age is shown in Table 1. Out of 70 patients, 12 (or 17.1%) were found to be between the age group of 30 and 40 years. 33 (47.1%) of the cases were in the age group of 51–60 years, while 25 (35.75%) of the cases were in the 41–50 years age group. The distribution of healthy controls is shown in Table 2. Out of 70 controls, 16 (22.8%) belonged to the 30–40 year age range, while 27 (38.5%) each belonged to the 41–50 year and 51–60 year age ranges.

The distribution of the study population by BMI is shown in Table 3. In this study, 21 (30%) patients out of 70 had normal range BMIs between 18 and 24.99, while the majority 37(52.85%) cases were overweight with BMIs between 25 and 29.99 and 11(15.71%) cases of diabetes patients were obese (BMI 30 and above). Our results are consistent with those of Williams et al., who demonstrated that obesity was independently connected to hs-CRP and that a rise in hs- CRP is related to a rise in BMI[33]. Similar to this, Jaiswal et al. (2012) showed in their study that patients with poor glucose tolerance had significantly higher levels of high sensitivity CRP[34,35]. According to this study, patients with T2DM had significantly higher levels of glycemic markers than healthy controls, with a p-value of 0.001. In the current investigation, we also noticed that patients with T2DM had significantly higher levels of hs-CRP, with a mean value of 2.49 ± 1.15mg/L compared to controls, who had a mean value of 1.22 ± 0.54mg/L

($p<0.001$) [Table 6]. Our research findings are consistent with those of Pfutzner and Forst (2006) and Stehouwer et al. (2002) [36,37].

It is noteworthy that persistent hyperglycemia encourages the release of different inflammatory cytokines (IL 6; TNF) and causes the liver to secrete acute phase reactants, which in turn causes hs-CRP to rise along with fasting plasma glucose levels to rise [38].This study found a substantial relationship between BMI and blood hs-CRP levels in T2DM similar to the findings of other studies [39,40]. It has been hypothesized that obesity and hyperglycemia create oxidative stress,[41] which leads to the production of free radicals in diabetic individuals who may damage cell membranes. These free radicals are linked to an increase in hs-CRP, a mediator of inflammation. [42]. Our results are consistent with those of Laaksonan et al.8, who in their prospective analysis hypothesised that a high hs-CRP level is linked to a higher risk of acquiring type 2 diabetes. According to Festa et al., higher hs-CRP levels have been linked to obesity, insulin resistance, and glucose intolerance, indicating that inflammation may also play a role in the development of type 2 diabetes [43,44]. In their work, Dr. Vijay Lal demonstrated that a rise in HbA1C is significantly correlated with an increase in hs-CRP levels [45].

Additionally in this study, compared to controls, patients with Type 2 DM exhibited higher levels of Total Cholesterol, LDL, VLDL, and TG. In diabetic cases, the mean serum cholesterol level was 204.30 ± 38.27 mg/dl, compared to 168.59 ± 38.24 mg/dl in control groups. The mean level of serum LDL in diabetic patients was 117.45 ±38.59 mg/dl, compared to 90.44 ± 33.14 mg/dl in controls. When compared to controls, who had a mean value of 30.35 ± 12.67mg/dl, diabetic cases' mean serum VLDL levels were higher at 41.48 ±11.55 mg/dl. The results of TG likewise showed a similar pattern, with mean values of 151.77 ± 63.38 mg/dl in individuals without diabetes and 207.44 ± 57.77 mg/dl in patients with diabetes. [Table 5]. A risk factor for acute coronary syndrome and atherosclerosis is low-grade inflammation. Acute phase proteins, such as hs-CRP, are produced soon after liver cells cause inflammation. The local secretion of a number of cytokines, including IL-1, IL-6, and TNF-alpha, in the region of the injured tissue controls the amount of CRP produced [46].

The onset and progression of atherosclerosis are correlated with LDL-C, triglycerides, and total cholesterol [47]. Low-density lipoprotein cholesterol serves as the body's transporter of cholesterol and other lipids (LDL-C). Once oxidised, LDL-C is known as tiny dense LDL, which can cause a localised, low-grade inflammatory response that results in the production of cytokines. When monocytes phagocytose oxidised LDL, they turn them into foam cells with a lipid core, which is the first step in the creation of atherosclerotic plaque. Additionally, the release of IL-6 by adipose tissue can be triggered by the excessive loading of triglycerides in adipose tissue seen in obesity [48]. On the other hand, because HDL-C is involved in reverse cholesterol transfer, having high levels of serum HDL-C is linked to a lower risk of developing atherosclerotic disease. Therefore, it is thought that HDL-C particles are anti-atherogenic and inhibit the pathways of thrombosis, inflammatory response, and LDL-C oxidation [49].

In their investigation, Dr. Shubham Bhaskar et al. found a statistically significant positive correlation (p= 0.05) between CRP and total cholesterol and LDL and triglycerides. Negative correlation existed between HDL cholesterol and CRP. [38]. hs-CRP levels and triglycerides were reported to be positively associated by Ana et al. like earlier studies, this one also revealed a favourable association [50].These results were similar the results of study conducted by Palvasha et al.[51]. According to the concentrations of serum hs-CRP, study participants were divided into three groups as shown in Table 7. Eight of the cases (n=70) had low risk hs-CRP values of less than 1 mg/L, forty had intermediate risk, and twenty-two had high risk of MI with hs-CRP values > 3mg/L.

We also discovered that patients with hs-CRP levels >3 mg/L had values for BMI, TC, LDL, and TG that were significantly higher than those with hs-CRP levels 1-3 mg/L, and even higher than those with hs-CRP levels 1 mg/L. [Table 8]. The serum level of LDL has been advised to be kept below 100 mg/dl in Type 2 Diabetes as it has been established as an independent marker of CVS risk [22]. In this study we observed that 25(37.14 %) cases with Serum LDL levels >100mg/dl have their hs-CRP levels between the range of 1-3mg/L(Intermediate risk) whereas 19(27.14 %) of the cases have their hs-CRP levels >3 mg/L. 15 (25.71%) out of 70 cases have their LDL levels <100mg/dl corresponding to which their hs-CRP values were more than 1mg/L. Therefore, measuring hs-CRP levels in diabetes patients on a regular basis will enable us to predict and delay CVD, even in those patients who have normal LDL levels and are thought to have low CVD risk. According to this present study not only does low-grade inflammation play a crucial part in the etiology of diabetes mellitus, but it also has a link to dyslipidemia in diabetics. Elevated hs-CRP levels have been linked to obesity and dyslipidemia in Type 2 diabetics. Our study suggests assessing its levels along with lipid profile so that we can predict CVD early and better take appropriate preventive measures.

Conclusion

According to the study data, patients with T2DM had significantly higher levels of both hs-CRP and lipids than the controls. Additionally, it confirms that there was a significant association between BMI, serum LDL-C, total cholesterol, and triglycerides in people with higher hs-CRP levels >3 mg/L (high-risk patients), indicating that people with T2DM may have low-grade systemic inflammation. These findings suggest that hs-CRP may be useful for atherosclerosis risk assessment and screening in patients with T2DM. hs-CRP has the potential to serve as a marker of future risk of cardiovascular disease as a categorical variable. Therefore, screening of T2DM for serum hs-CRP levels and lipid profile at an earlier stage may be done to identify those patients who are at a higher risk of developing atherosclerosis or cardiovascular events in the future.

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