ISSN: 0975-3583,0976-2833 VOL16, ISSUE 01, 2025

Correlation between Glycated Hemoglobin, Non-HDL Cholesterol, hs-CRP and Fructosamine in Diabetic and Healthy Individuals

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Abstract:

Background: Type 2 Diabetes Mellitus (T2DM) is a chronic metabolic disorder characterized by hyperglycemia, insulin resistance, and altered lipid metabolism, increasing the risk of cardiovascular diseases and other complications. Monitoring glycemic control through HbA1c is essential, but it may not fully capture the broader metabolic disturbances associated with T2DM, including lipid abnormalities and systemic inflammation. This study aims to explore the correlations between HbA1c and various metabolic parameters in T2DM patients, including fasting blood sugar (FBS), lipid profile (total cholesterol, LDL-C, HDL-C, non-HDL-C, triglycerides), high-sensitivity C-reactive protein (hs-CRP), and fructosamine.

Methods: A case-control study was conducted at Index Medical College, Indore, involving 105 Type 2 diabetes patients (cases) and 105 age- and gender-matched healthy individuals (controls). The study measured various parameters, including HbA1c, FBS, lipid profile components, hs-CRP, and fructosamine levels.Pearson's correlation coefficients were calculated to evaluate the strength and direction of relationships between HbA1c and these parameters. Additionally, comparisons were made across three glycemic control groups: normal (HbA1c $\leq$ 6.4%), good (HbA1c 6.5-8%), and poor (HbA1c $\geq$ 8%), using ANOVA for statistical significance.

Results: The study found statistically significant positive correlations between HbA1c and FBS ($r = 0.626$), non-HDL-C ($r = 0.662$), total cholesterol ($r = 0.664$), LDL-C ($r = 0.545$), hs-CRP ($r = 0.487$), and fructosamine ($r = 0.881$) (all $p < 0.05$). HDL-C and triglycerides showed weak or no significant correlation with HbA1c ($p > 0.05$). Furthermore, significant differences in lipid profile, triglycerides, hs-CRP, and fructosamine were observed between the three glycemic control groups, with poorer glycemic control associated with worse lipid and inflammatory markers.

Conclusion: The findings highlight the complex interplay between glycemic control and metabolic disturbances in T2DM. HbA1c is significantly correlated with various lipid fractions and inflammatory markers, suggesting that comprehensive metabolic monitoring is essential for optimizing diabetes management. Additionally, fructosamine emerged as a strong correlate of HbA1c, further supporting its role in evaluating short-term glycemic control. These results underscore the need for integrated approaches in managing T2DM, targeting both glycemic control and cardiovascular risk factors.

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Keywords: Type 2 diabetes mellitus, HbA1c, lipid profile, fructosamine, high-sensitivity C-reactive protein, glycemic control.

Introduction:

Type 2 Diabetes Mellitus (T2DM) is a chronic metabolic disorder characterized by insulin resistance and impaired insulin secretion, resulting in persistent hyperglycemia. It is a major global health concern, as it increases the risk of cardiovascular diseases, kidney failure, and neuropathy. Effective management of T2DM requires maintaining optimal glycemic control to prevent long-term complications.[1] The International Diabetes Federation Atlas 2015 reported that around 69.2 million people in India were affected by type 2 diabetes.[2] One of the most commonly used biomarkers for monitoring long-term blood glucose levels is glycated hemoglobin (HbA1c). HbA1c provides an integrated measure of blood glucose over the previous 2-3 months, and it is widely regarded as a reliable indicator of chronic hyperglycemia in clinical practice.[1] This test is preferred for its convenience, as it can be done at any time of the day without requiring fasting. In addition to monitoring glycemic control, HbA1c is increasingly used for diagnosing diabetes and screening individuals at high risk of developing the condition.[3,4,5]

However, HbA1c alone does not fully capture the metabolic derangements that often accompany T2DM. In addition to dysregulated glucose metabolism, patients with T2DM frequently exhibit abnormal lipid profiles, characterized by elevated levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and triglycerides, as well as reduced levels of high-density lipoprotein cholesterol (HDL-C). These lipid abnormalities contribute to an increased risk of cardiovascular diseases, which is a leading cause of morbidity and mortality in diabetic individuals.[6]

Non-high-density lipoprotein cholesterol (Non-HDL-C) is another important marker in diabetic patients[7]. It is determined by subtracting HDL cholesterol (HDL-C) from total cholesterol (TC).[8] Non-HDL-C encompasses LDL cholesterol (LDL-C) as well as other potentially atherogenic lipoproteins such as VLDL, IDL, and Lp(a). In diabetic individuals, who often experience atherogenic dyslipidemia characterized by low HDL-C and high triglycerides, non-HDL-C serves as a more accurate predictor of cardiovascular risk than LDL-C alone. Many individuals with diabetes fail to reach the recommended targets for both non-HDL-C and LDL-C, increasing their risk for cardiovascular events.[9]

Systemic inflammation, indicated by biomarkers such as high-sensitivity C-reactive protein (hs-CRP), plays a crucial role in the pathogenesis of atherosclerosis and insulin resistance, further complicating the management of T2DM[10] Elevated CRP levels have been linked to an increased risk of atherosclerosis, with uncontrolled Type 2 diabetes mellitus (T2DM) contributing to higher CRP levels.[11,12,13]The development of high-sensitivity CRP (hs-CRP) testing enables the detection of mild CRP elevations, which are indicative of chronic low-grade inflammation.[14]

In addition to HbA1c, fructosamine has emerged as an alternative marker for assessing short-term glycemic control. Fructosamine reflects the average blood glucose level over the previous 2-3 weeks, providing a more immediate assessment of glycemic control than HbA1c.[15] Recent studies have suggested that fructosamine may correlate strongly with HbA1c, making it a valuable adjunct in diabetes management, particularly in settings where HbA1c measurement is less reliable, such as in individuals with hemoglobinopathies or those with renal

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impairment.[16,17,18,19] Higher fructosamine levels have been connected to a greater risk of cardiovascular morbidity and mortality, not only in individuals with diabetes but also in those with normal blood sugar levels.[20,21,22]

Given the importance of comprehensive metabolic monitoring in T2DM, the aim of this study was to investigate the correlations between HbA1c and various metabolic parameters, including fasting blood sugar (FBS), lipid profile components (total cholesterol, LDL-C, HDL-C, non-HDL-C), triglycerides, hs-CRP, and fructosamine in patients with T2DM. Previous research has established that HbA1c is positively correlated with several lipid fractions and inflammatory markers, indicating that better glycemic control may be associated with improved lipid profiles and lower levels of systemic inflammation.[6,11]

Our results demonstrate statistically significant positive correlations between HbA1c and FBS, various lipid fractions (total cholesterol, LDL-C, non-HDL-C), triglycerides, and hs-CRP. The strongest correlation was observed between HbA1c and fructosamine, further supporting the utility of fructosamine as a marker of glycemic control. In addition, we evaluated the variation of these parameters across three categories of glycemic control—normal (HbA1c $\leq$ 6.4%), good (HbA1c 6.5-8%), and poor (HbA1c $\geq$ 8%)—revealing significant differences in lipid and inflammatory markers across these groups. These findings underscore the complex interplay between glucose metabolism, lipid abnormalities, and inflammation in T2DM and highlight the importance of a multifaceted approach to diabetes management that incorporates both glycemic control and monitoring of cardiovascular risk factors.

This study enhances our understanding of the connections between HbA1c and other metabolic factors, contributing to the expanding body of research on Type 2 diabetes. It underscores the importance of comprehensive monitoring and management of blood glucose, lipid levels, and inflammation. By optimizing these factors, we can help prevent the long-term complications commonly associated with the condition.

Materials and Methods

This case-control study was conducted at the Department of Biochemistry, Index Medical College and Hospital, Indore, Madhya Pradesh, India, from December 2022 to December 2023. A total of 210 participants were included, consisting of 105 patients with type 2 diabetes mellitus (T2DM) and 105 age- and gender-matched healthy controls, aged between 30 to 60 years. The study included newly diagnosed T2DM patients as well as individuals with known T2DM, whether treated with oral hypoglycemic agents, insulin, or hypolipidemic drugs, or not on treatment. Healthy controls were matched for age and gender with the T2DM patients.

Exclusion criteria included individuals with type 1 diabetes mellitus, females on oral contraceptive pills, anemia, nephrotic syndrome, chronic renal failure, cirrhosis, liver diseases, pregnancy, thyroid disorders, hemoglobinopathies, recent myocardial infarction (MI), or those with acute illnesses. Furthermore, patients who had undergone hs-CRP testing and were prescribed antibiotics, antivirals, or antimycotics within the previous 7 days were excluded, as these medications could indicate infection, which might be the cause of elevated hs-CRP levels.

The diagnosis of T2DM was confirmed based on the criteria set by the American Diabetes Association (ADA), which includes HbA1c levels $\geq$6.5% and fasting blood sugar (FBS) levels $\geq$126 mg/dl.[23]

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Fasting blood sugar and serum fasting lipid profiles were measured using Hexokinase[24,25,26] and other enzymatic methods[27,28,29,30] respectively, on a fully automated analyzer. HbA1c levels were estimated using the Bio-Rad D-10 HbA1c program. hs-CRP and fructosamine were measured by particle-enhanced immunoturbidimetric assay[31,32] and a colorimetric test involving reaction with nitroblue tetrazolium,[33,34,35] respectively.

Statistical analysis was carried out using SPSS Software, version 20.0 for Windows. Continuous variables were expressed as mean ± standard deviation (S.D.), and qualitative data were presented as percentages. The independent t-test was used to compare parameters between the case and control groups, with a p-value of <0.05 considered statistically significant.

Results

In this study a total 210 patients were evaluated. The overall distribution of patients is as shown in table 1.

Table 1: Distribution of patients by gender

Gender	Number of cases	Number of controls	Percentage (%)
Male	60	60	57.14
Female	45	45	42.86
Total	105	105	100

“Correlation (r-value) between HbA1c and FBS was found to be 0.626 and it was statistically significant with p< 0.05” (Graph 1).

Graph-1: Scatter graph of correlation between “HbA1c” (%) and “FBS” (mg/dl) in all Type II DM patients

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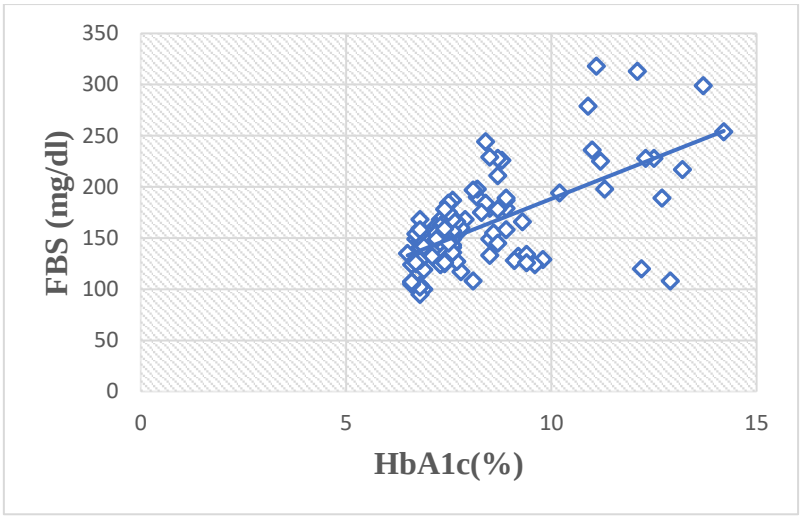
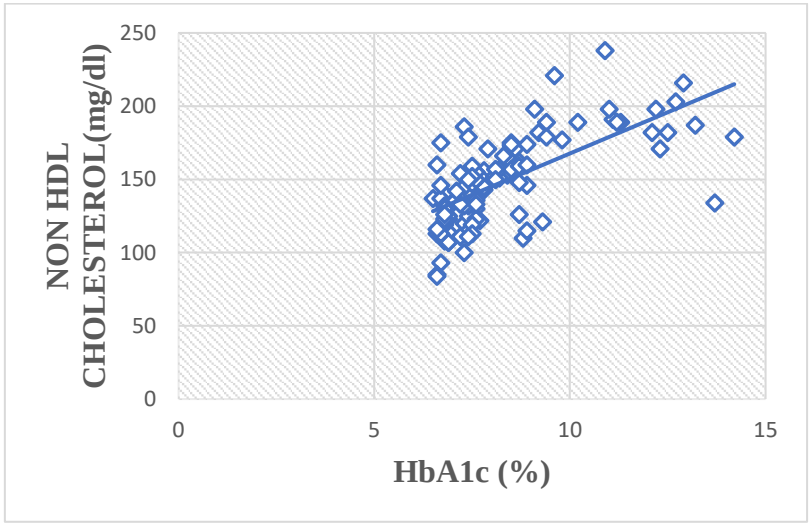


"Correlation (r-value) between HbA1c and Non- HDL cholesterol was found to be 0.662 and it was statistically significant with p< 0.05" (Graph 2)

Graph-2: Scatter graph of correlation between "HbA1c" (%) and "Non-HDL cholesterol" (mg/dl) in all Type II DM patients.



"Correlation (r-value) between HbA1c and Total cholesterol was found to 0.664 and it was statistically significant with p< 0.05" (Graph 3)

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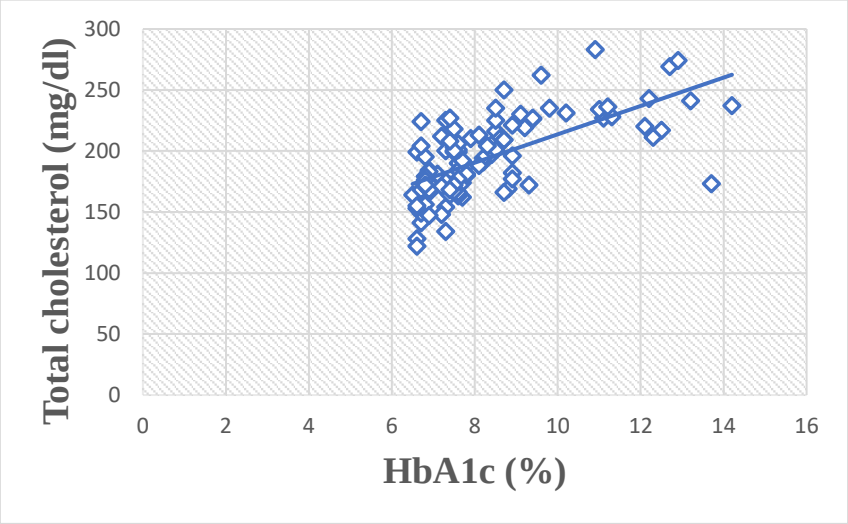
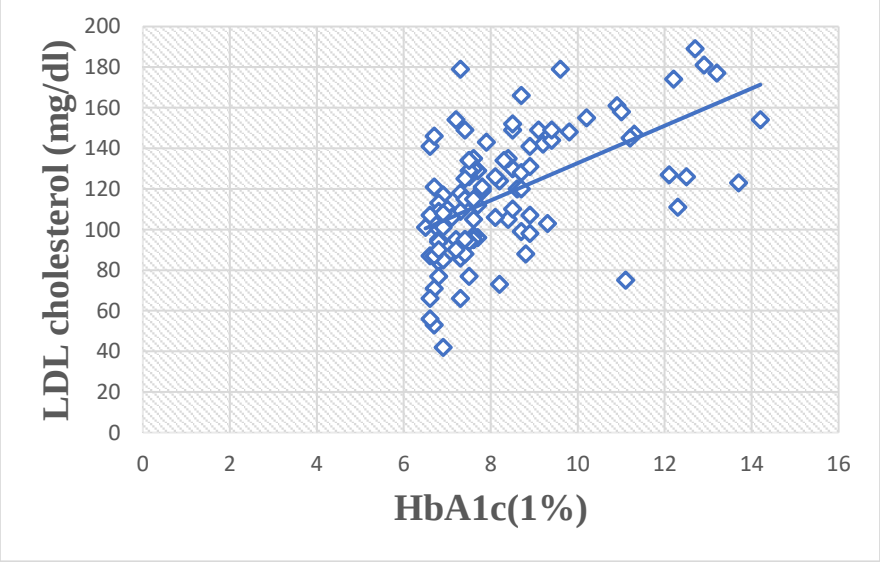
Graph-3: Scatter graph of correlation between "HbA1c" (%) and "total cholesterol" (mg/dl) in all Type II DM patients.



"Correlation (r-value) between HbA1c and LDL-C was found to be 0.545 and it was statistically significant with p< 0.05" (Graph 4)

Graph-4: Scatter graph of correlation between "HbA1c" (%) and "LDL cholesterol" (mg/dl) in all Type II DM patients.



"Correlation (r-value) between HbA1c and HDL-C was found to be 0.060 and it was not statistically significant with p< 0.05" (Graph 5)

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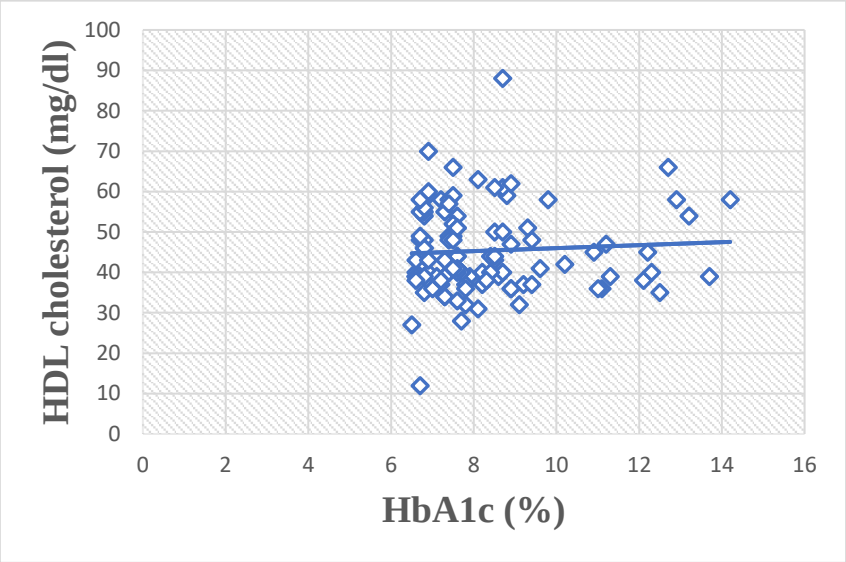
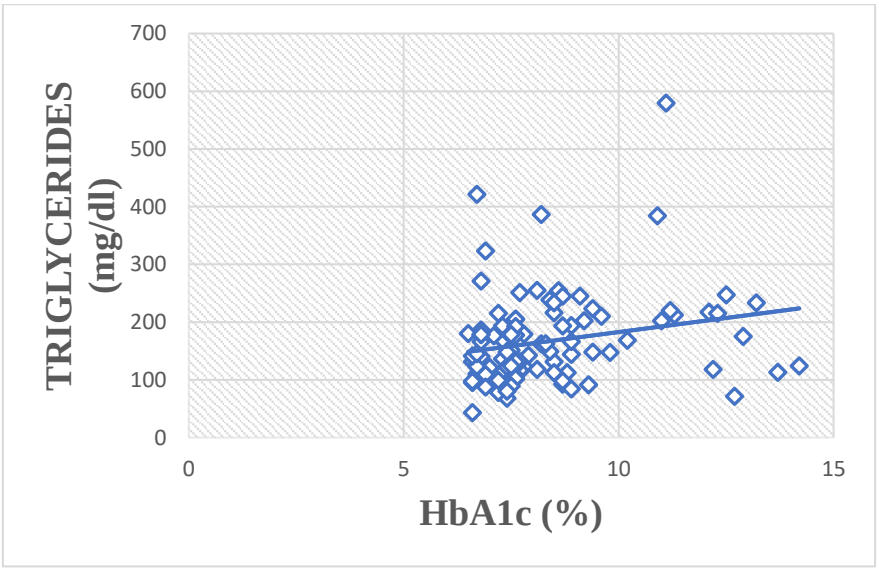
Graph-5: Scatter graph of correlation between "HbA1c" (%) and "HDL cholesterol" (mg/dl) in all Type II DM patients.



"Correlation (r-value) between HbA1c and triglycerides was found to be 0.216 and it was not statistically significant with p< 0.05" (Graph 6)

Graph-6: Scatter graph of correlation between "HbA1c" (%) and "triglycerides" (mg/dl) in all Type II DM patients.



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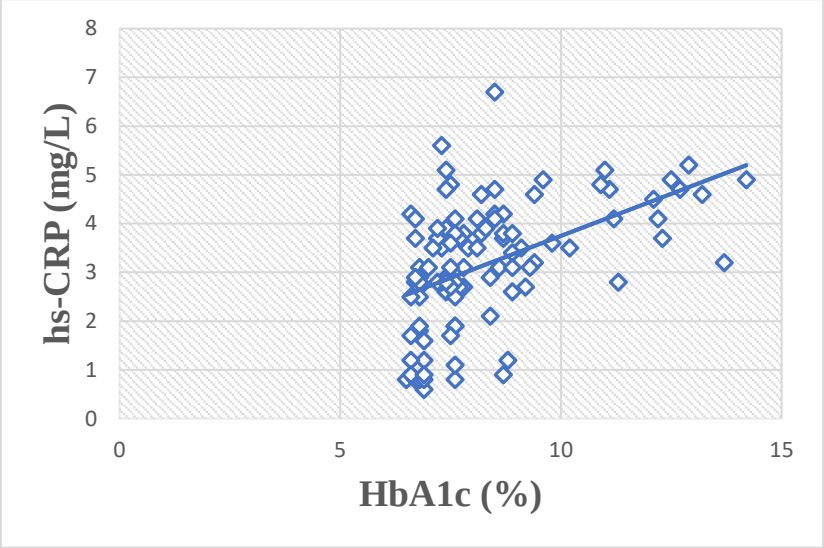
"Correlation (r-value) between HbA1c and hs-CRP was found to be 0.487 and it was statistically significant with p< 0.05" (Graph 7)

Graph-7: Scatter graph of correlation between "HbA1c" (%) and "hs-CRP" (mg/L) in all Type II DM patients.



"Correlation (r-value) between HbA1c and Fructosamine was found to be 0.881 and it was statistically significant with p< 0.05" (Graph 8)

Graph-8: Scatter graph of correlation between "HbA1c" (%) and "Fructosamine" (/L) in all Type II DM patients.

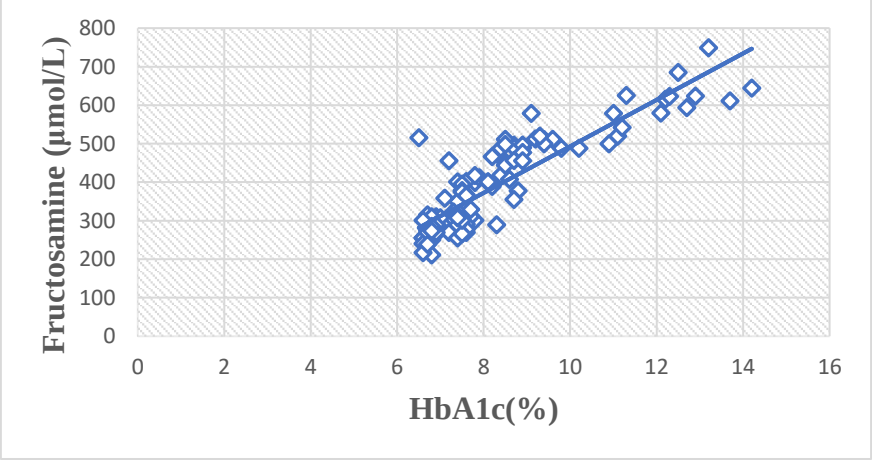


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Table-2: Comparison of mean, S.D, f-value and p-value of measured parameters of normal, good and poor glycemic control.

PARAMETER	Group A (Normal) HbA1c ≤6.4%		Group B (Good) HbA1c 6.5-8%		Group C (Poor) HbA1c ≥ 8%			
	Mean	SD	Mean	SD	Mean	SD	f-value	p-value
FBS (mg/dl)	104.9	13.3	141.7	22.2	190.4	53.8	139.6	< 0.0001*
HbA1c (%)	5.8	0.4	7.2	0.4	9.9	1.8	342.5	< 0.0001*
TC (mg/dl)	158.2	34.8	177.7	23.4	217.5	27.9	58.1	< 0.0001*
LDL-C (mg/dl)	86.7	30.0	105.6	25.5	133.9	27.9	43.2	< 0.0001*
HDL-C (mg/dl)	46.2	9.6	44.7	10.2	46.3	11.5	0.5	0.63
Triglyceride (mg/dl)	136.6	54.2	147.9	61.0	192.7	92.0	11.35	< 0.0001*
Non-HDL-C (mg/dl)	112.0	32.6	133.0	21.6	171.2	27.1	65.6	< 0.0001*
Hs-CRP (mg/L)	0.97	0.74	2.7	1.2	3.8	1.0	153.9	< 0.0001*
Fructosamine (µmol/L)	258.9	31.7	309.6	57.5	507.9	92.0	299.0	< 0.0001*

p value <0.05

The study compared various health parameters across three groups based on HbA1c levels: Group A (Normal) HbA1c ≤ 6.4%, Group B (Good) HbA1c 6.5-8%, and Group C (Poor) HbA1c ≥ 8%. Fasting Blood Sugar (FBS) levels significantly increased with increasing HbA1c. Group A had a mean FBS of 104.9 mg/dl (SD = 13.3), Group B had a mean of 141.7 mg/dl (SD = 22.2), and Group C had the highest mean FBS of 190.4 mg/dl (SD = 53.8), with a significant difference across the groups (F-value = 139.6, $p < 0.0001$). HbA1c levels were significantly higher in Groups B and C compared to Group A. The mean HbA1c was 5.8% (SD = 0.4) in Group A, 7.2% (SD = 0.4) in Group B, and 9.9% (SD = 1.8) in Group C, with a significant difference between the groups (F-value = 342.5, $p < 0.0001$). Total Cholesterol (TC) levels significantly increased from Group A to Group C, with Group A having a mean of 158.2 mg/dl (SD = 34.8), Group B having 177.7 mg/dl (SD = 23.4), and Group C having 217.5 mg/dl (SD = 27.9). The ANOVA test revealed significant differences (F-value = 58.1, $p < 0.0001$). LDL-C levels showed a similar trend to TC, with Group A having 86.7 mg/dl (SD = 30.0), Group B having 105.6 mg/dl (SD = 25.5), and Group C having 133.9 mg/dl (SD = 27.9). The difference between the groups was highly significant (F-value = 43.2, $p < 0.0001$). There was no significant difference in High-Density Lipoprotein Cholesterol (HDL-C) levels across the groups, with Group A having 46.2 mg/dl (SD = 9.6), Group B having 44.7 mg/dl (SD = 10.2), and Group C having 46.3 mg/dl (SD = 11.5), and a non-significant p-value of 0.63. Triglyceride

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levels significantly increased from Group A to Group C. Group A had a mean of 136.6 mg/dl (SD = 54.2), Group B had 147.9 mg/dl (SD = 61.0), and Group C had 192.7 mg/dl (SD = 92.0), with a significant difference across the groups (F-value = 11.35, $p < 0.0001$). Non-HDL cholesterol levels followed a similar trend to TC and LDL-C, with Group A having 112.0 mg/dl (SD = 32.6), Group B having 133.0 mg/dl (SD = 21.6), and Group C having 171.2 mg/dl (SD = 27.1). Significant differences were found between the groups (F-value = 65.6, $p < 0.0001$). Hs-CRP levels significantly increased with higher HbA1c levels. Group A had a mean of 0.97 mg/L (SD = 0.74), Group B had 2.7 mg/L (SD = 1.2), and Group C had 3.8 mg/L (SD = 1.0). The differences were highly significant (F-value = 153.9, $p < 0.0001$). Fructosamine levels also showed significant increases with higher HbA1c levels. The mean fructosamine was 258.9 µmol/L (SD = 31.7) in Group A, 309.6 µmol/L (SD = 57.5) in Group B, and 507.9 µmol/L (SD = 92.0) in Group C, with a significant difference between the groups (F-value = 299.0, $p < 0.0001$). The results demonstrate a clear association between higher HbA1c levels and worsening metabolic parameters, including increased FBS, cholesterol (TC, LDL-C, non-HDL-C), triglycerides, Hs-CRP, and fructosamine. No significant difference was observed in HDL-C levels across the groups. These findings underscore the importance of maintaining optimal HbA1c levels to prevent adverse changes in lipid metabolism and inflammation.

Discussion:

This study investigated the relationships between HbA1c and several metabolic parameters, including fasting blood sugar (FBS), lipid profile (total cholesterol, LDL-C, HDL-C, non-HDL-C, triglycerides), high-sensitivity C-reactive protein (hs-CRP), and fructosamine, in patients with Type 2 Diabetes Mellitus (T2DM). Our findings highlight several important insights into the metabolic disturbances associated with T2DM and emphasize the value of comprehensive monitoring of both glycemic control and related risk factors in the management of this disease.

The correlation between HbA1c and FBS was moderate ($r = 0.626$), consistent with previous studies showing that elevated HbA1c levels are typically associated with higher fasting glucose concentrations.[3,4] This positive correlation supports the utility of HbA1c as a long-term indicator of glycemic control. In addition, the significant correlations between HbA1c and lipid parameters, including total cholesterol, LDL-C, and non-HDL-C (r-values of 0.664, 0.545, and 0.662, respectively), suggest that poor glycemic control in T2DM is closely linked to lipid abnormalities, particularly elevated atherogenic lipoproteins. These findings are in line with research showing that hyperglycemia contributes to the dysregulation of lipid metabolism, increasing the risk of cardiovascular diseases in T2DM patients.[36,37]

Interestingly, HDL-C did not show a significant correlation with HbA1c ($r = 0.060$, $p = 0.63$), suggesting that while dyslipidemia is a hallmark of T2DM, the relationship between HbA1c and HDL-C is weak or non-existent in this population. This may reflect the complex and multifactorial nature of HDL-C regulation, which is influenced by various factors beyond glycemic control, such as genetic predisposition, physical activity, and medication use. Furthermore, triglycerides showed a weak, non-significant correlation with HbA1c ($r = 0.216$, $p > 0.05$), which may be attributed to the variability in triglyceride metabolism among individuals with T2DM. These findings are not similar to those reported in other studies, which may have observed stronger or more significant correlations between HbA1c and lipid levels, potentially due to differences in study design, population characteristics, or other confounding factors.[37,38]

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Our study also found a moderate positive correlation between HbA1c and hs-CRP ($r = 0.487$, $p < 0.05$), indicating a link between chronic inflammation and poor glycemic control in T2DM. Chronic low-grade inflammation is considered a key factor in the pathogenesis of insulin resistance and the development of cardiovascular complications in diabetic patients. Elevated hs-CRP levels are associated with an increased risk of atherosclerosis and other cardiovascular events, which are particularly common in patients with poorly controlled diabetes.[39] Therefore, hs-CRP could serve as a valuable biomarker for monitoring inflammatory status and assessing cardiovascular risk in T2DM patients, especially those with suboptimal glycemic control.

One of the most significant findings of this study was the strong correlation between HbA1c and fructosamine ($r = 0.881$, $p < 0.05$), which suggests that fructosamine could be a reliable alternative marker for assessing short-term glycemic control in T2DM patients. Fructosamine, a marker of serum glycated proteins, reflects blood glucose concentrations over the previous 2-3 weeks, making it particularly useful in situations where HbA1c might be less accurate, such as in patients with hemoglobinopathies or those undergoing rapid changes in glucose control.[40,41] The strong correlation between these two markers reinforces the potential of fructosamine as an adjunct to HbA1c for more immediate assessments of glycemic management

Our analysis of the different glycemic control groups—normal (HbA1c ≤ 6.4%), good (HbA1c 6.5-8%), and poor (HbA1c ≥ 8%)—showed significant differences in metabolic parameters, particularly in lipid profiles, triglycerides, hs-CRP, and fructosamine. These findings reflect the established notion that suboptimal glycemic control exacerbates lipid and inflammatory disturbances in T2DM, thereby increasing the risk of cardiovascular complications. The significant increase in total cholesterol, LDL-C, non-HDL-C, triglycerides, hs-CRP, and fructosamine from the normal to the poor glycemic control group highlights the importance of maintaining strict glycemic control to reduce the risk of these complications.[37,38,39,40]

Conclusion

This study emphasizes the complex interplay between glycemic control and metabolic disturbances in Type 2 Diabetes Mellitus. Our findings suggest that HbA1c is significantly correlated with various lipid fractions and inflammatory markers, reinforcing its role as a crucial measure of long-term glycemic control. Furthermore, fructosamine appears to be a strong correlate of HbA1c, supporting its use as a complementary tool for monitoring short-term glucose management. The study indicates that HbA1c, non-HDL cholesterol, fructosamine, and hs-CRP are valuable markers in assessing metabolic health and risk for cardiovascular complications. HbA1c offers a reliable reflection of long-term glucose control, while non-HDL cholesterol serves as a comprehensive measure of atherogenic lipoproteins. Fructosamine provides insight into short-term glycemic fluctuations, complementing HbA1c. Additionally, hs-CRP, a marker of inflammation, plays a crucial role in identifying individuals at increased risk for cardiovascular events. Together, these markers offer a multifaceted approach to evaluating metabolic health and could help guide early interventions for high-risk populations.These results underline the importance of comprehensive metabolic monitoring in T2DM management to reduce the risk of cardiovascular disease and other complications, ultimately improving patient outcomes.

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