Research article

Relationship between serum high-sensitivity C-reactive protein (hs-CRP) and glycated hemoglobin (HbA1c) in South Indian population

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ABSTRACT

Introduction and Aim: Cardiovascular disease are a leading cause of death in the world. Atherosclerosis plays the most important role in its pathophysiology. It is a slowly progressing chronic inflammatory process resulting in increased levels of inflammatory markers in serum. hs-CRP is a novel biomarker of coronary heart disease risk prediction. Type 2 diabetes mellitus individuals are at an increased risk of developing cardiovascular diseases. In this study, we aim to find the association of HbA1c with hs-CRP in the South Indian population.

Materials and Methods: This was a retrospective study. The study participants were categorised into 3 groups based on their serum hs-CRP levels: Group 1 with hs-CRP < 1.0 mg/L; group 2 with hs-CRP 1.0 – 3.0 mg/L and group 3 with hs-CRP > 3.0 mg/L. The sample size was estimated to be 40 for each group. Age, fasting blood glucose, postprandial blood glucose, HbA1c, hs-CRP, total count, and ESR were collected. Statistical analyses were performed with SPSS version 16.0.

Results: Age showed no significant difference among the groups. FBS, PPBS, HbA1c, TLC, and ESR showed a significant difference among the 3 groups. TLC, FBS, PPBS, and HbA1c had a significant positive correlation with hs-CRP.

Conclusion: hs-CRP has a statistically significant positive correlation with HbA1c, fasting blood sugar, and postprandial blood sugar Additionally, we also observed that total leukocyte count had a significant positive correlation with hs-CRP and HbA1c. Hence, our results show that impaired glycemic control is associated with an increased risk of developing cardiovascular diseases.

Keywords: HbA1c; hs-CRP; cardiovascular risk.

INTRODUCTION

Chronic inflammation is defined as an inflammation lasting for prolonged periods; say for several months to years. Chronic inflammation can be due to failure in eliminating the inflammation causing agent like agents causing infections, or due to chronic exposure to an irritant or foreign material; autoimmune disorders, or recurrent episodes of acute inflammation. Increased production of free radicals, advanced glycation end products, uric acid crystals, oxidized lipoproteins resulting in oxidative stress leading to mitochondrial dysfunction can also mediate the chronic inflammatory process (1).

Cardiovascular disease is one of the leading causes of death in the world. "Global Burden of Disease Study" has shown that the cardiovascular disease death rate is 272 per 10000 population in India. It is much higher than the global average of 235 deaths per 10000 (2). According to 2016 data in India, 28.1% of total deaths and 14.1% of total disability-adjusted life years were contributed by cardiovascular diseases (3).

Though cardiovascular diseases develop due to different aetiologies, atherosclerosis plays the most important role in its pathophysiology. The medium and the large sized arteries are affected by atherosclerosis. Atherosclerosis is a chronic inflammatory disease designated by the deposition of cholesterol and cholesterol esters from the plasma lipoproteins into the artery wall. An atherosclerotic plaque has three components namely: macrophages and smooth muscle cells forming the first component, connective tissue matrix forming the second component and foam cells formed by accumulation of intracellular lipid in macrophages forming the third component (4).

Low-density lipoproteins (LDL) deposits lipids into the atherogenic plaque. LDL is oxidized and is also taken up by macrophages or monocytes. The accumulation of lipids within macrophages results in the formation of foam cells. This deposition of foam cells in the arterial wall results in a fatty streak; the first visible lesion of atherosclerosis. Foam cells in turn secrete cytokines and other inflammatory mediators.

It is initiated with the over-expression of adhesion molecules of the endothelial cell like VCAM-1. Increased VCAM-1 expression recruits T-cells and monocytes to the site of injury. This results in the increase in monocyte chemo-attractant protein-1 (MCP-1) release leading to an exaggerated inflammatory cascade. This causes further recruitment of leukocytes and increased proliferation of the

smooth muscle cells to this site. The recruited monocytes activate enzymes like matrix metalloproteinase (MMP) which degrades the matrix resulting in further release of inflammatory mediators like interleukin-1, TNF-α, interleukin-6, CD-40, etc… and cytokines. Hence, atherogenesis is a slowly progressing chronic inflammatory process. Activation of this inflammatory cascade results in increased levels of inflammatory markers in serum (4).

'Diabetes mellitus is a group of metabolic disorders that share the phenotype of hyperglycemia, resulting from defects in insulin secretion, insulin action, or both'. The burden of diabetes mellitus is increasing rapidly around the world due to rapid urbanization, sedentary lifestyle, and increased prevalence of obesity. Around the world, 537 million people are living with diabetes mellitus today. India is home to the second-largest number of adults with diabetes mellitus. It is a growing challenge in India with 74 million people affected (5).

Previous studies have shown an increased risk of developing cardiovascular disease in individuals with Type 2 diabetes mellitus. This increased risk is multifactorial. Hyperglycemia resulting in increased free fatty acids, insulin resistance resulting in increased oxidative stress, increased advanced glycation end products and disruption in protein kinase pathway results in elevated cardiovascular disease risk. In type 2 diabetes mellitus patients, adipose tissue secretes cytokines contributing to chronic inflammation and thrombosis. Also, dyslipidemia accompanying the type 2 diabetes mellitus contributes to atherosclerosis (7).

A significant association between low-level chronic inflammation and the development of insulin resistance and type 2 diabetes mellitus have been shown by many recent studies. Insulin binds to insulin receptors which in turn phosphorylates and activates the insulin receptor substrates namely IRS-1and IRS-2. The IRS proteins in-turn will activate the phosphoinositol-3- kinase pathway leading to the uptake of glucose and its metabolism. Insulin resistance is defined as the condition when tissues (especially adipose tissue) are unable to respond to insulin resulting in decreased cellular uptake of glucose. The development of insulin resistance is multifactorial. TNF- α, an inflammatory mediator mediates insulin resistance. TNF- α binds to TNF receptors resulting in serine phosphorylation of IRS-1 attenuating the insulin response. Leptin, interleukins, MCP-1, etc. also play an important role (8).

Several inflammatory markers are being used as predictors of cardiovascular risk as the relationship between inflammation and atherosclerotic plaque formation is well established. Adhesion molecules like E-selectin, intracellular adhesion molecule-1, vascular cell adhesion molecule-1, cytokines like TNF- α, interleukin-1β, IL-6, IL-8, total leukocyte count, ESR, and acute-phase reactants like fibrinogen, SAA, and CRP are being used (9).

C-reactive protein is an important acute-phase reactant, which is synthesized in the liver. Inflammatory mediators like TNF and IL-1, stimulate IL-6 which subsequently increase the production and release of CRP from the liver. CRP begins to rise 4-6 hours after the start of the infection and peaks in about 1-2 days. Previous studies have shown a positive association between the risk of future coronary artery disease and increased concentration of CRP. To use CRP for the above-mentioned purposes, assays with a detection limit <0.3mg/L are required. These assays are known as high-sensitivity C-reactive protein (hs-CRP) assays (10).

According to AHA and NACB, hs-CRP is the only inflammatory marker that fulfills the required criteria for a novel biomarker for risk prediction of coronary artery disease. AHA and NACB have also recommended to include hs-CRP in the global risk assessment of coronary artery disease (11,12). CRP is not just a marker, but it also plays an important role in the pathogenesis of atherosclerosis. It enhances the expression of monocyte chemoattractant protein-1, endothelial cell surface adhesion molecules, endothelin-1, and endothelial plasminogen activator inhibitor-1. Also, it reduces the activity of endothelial nitric oxide (12).

The American Heart Association has classified hs-CRP concentration into three categories based on the cardiovascular risk: (Table 1; 13)

Table 1: Cardiovascular risk based on hs-CRP level

Cardiovascular Risk	hs-CRP level
Low	< 1 mg/mL
Average	1 – 3 mg/mL
High	> 3 mg/mL

HbA1c indicates average value of glucose over the last 8 – 12 weeks. It is used to diagnose diabetes mellitus and to monitor glycemic control. HbA1c concentration is also used to predict the microvascular complications in individuals with type 2 diabetes mellitus. In this study, we aim to find the association of glycated hemoglobin with hs-CRP and also the role of HbA1c in cardiovascular risk prediction. The aim of the present study is to correlate the levels of serum high-sensitivity C-reactive protein (hs-CRP) with glycated hemoglobin (HbA1c) in the South Indian population.

MATERIALS AND METHODS

The study was conducted at a tertiary care hospital, Tamil Nadu. This was a retrospective observational study. The data for one year was collected.

The study population included individuals (20-70 years) who attended Master health check-up at Sri

Ramachandra Medical Centre in the year 2020 and have done hs-CRP and HbA1c. Children, adolescents, pregnant women, individuals with acute infection, and other comorbid conditions like chronic inflammatory diseases were ostracized from the study.

Based on the hs-CRP concentration, the participants in the study were categorised into the following three groups (Table 2):

Table 2: Category of participants based on hs-CRP concentration

Group	hs-CRP (mg/L)	No. of participants
1	< 1.0	40
2	1.0 – 3.0	40
3	> 3.0	40

Sample size calculation was done using CaTS power calculator software, California, USA. The sample size was estimated to be a minimum of 40 for each group. For the calculation of sample size, a two-sided test was employed. The study was conducted following the guidelines from the Institutional ethics committee. The study being retrospective, the requirement for consent was waived by the ethics committee.

The following information were extracted from the medical records: age, gender, past history, drug history, and diagnosis. Following data regarding laboratory investigations were collected, which included plasma blood glucose (fasting and postprandial), HbA1c, and total count to rule out acute infections and erythrocyte sedimentation rate was collected to rule out any ongoing chronic inflammatory conditions.

Fasting and post-prandial blood glucose were analysed in Beckman & Coulter AU 5800 and AU680 by the hexokinase method. Glycated haemoglobin was analysed by cation-exchange high-performance liquid chromatography in an auto analyser (Bio Rad variant II). hs-CRP was assayed by turbidimetric immunoassay in Beckman & Coulter AU 5800 and AU 680 in serum sample.

Social Sciences Statistical Software (SPSS) package for Windows, version 16.0 was used for statistical analysis. The data were tested for normality using Shapiro -Wilks test. Parameters with normal distribution were expressed as mean ±standard deviation and for the parameters with non-normal distribution median and interquartile range were used. ANOVA and Kruskal Wallis were performed for data with normal and non-normal distribution respectively and p-value of <0.05 was considered to be statistically significant. Post Havoc test was performed to check the significance between groups. Correlation analysis between the parameters was performed using Spearman's correlation (Fig. 1-3; Table 5, 6).

RESULTS

Table 3: Comparison of baseline characteristics between Group I(low-risk), Group II (intermediate-risk), and Group III (high-risk)

Parameter	Group I	Group II	Group III	*p*- value
Age (Years)	49.23 ± 12.063	51.05 ± 10.713	49.60 ± 9.145	0.724
TLC (cells/cmm)	6400 (5200 – 7150)	7300 (6600-7550)	7900 (6450 – 8850)	<0.001**
ESR (mm/h)	5 (3-7)	6 (4-7.5)	7 (4.5-8)	0.035*

Based on the normality of the variable, data is represented as Mean ± standard deviation (SD) or Median with Interquartile (IQR). Comparison done via ANOVA or Kruskal Wallis as the test of significance as applicable; * p <0.05Statistically significant; ** p <0.001Statistically significant; TLC- Total leukocyte count & ESR- Erythrocyte sedimentation rate.

There was no statistically significant difference in age among the three groups (*p* - >0.05). Though total leukocyte count and erythrocyte sedimentation rate was within the normal limits, there was a significant difference among the three groups (Table 3). The blood glucose levels of both fasting and post-prandial were significantly different among the groups (Table 4).

Table 4: Comparison of fasting blood glucose, postprandial blood glucose, and glycated hemoglobin between Group I (low-risk), Group II (intermediate-risk), and Group III (high-risk)

Parameter	Group I	Group II	Group III	*p*- value
FBS (mg/dL)	96 (93-99.75)	134 (111.25-184.25)	200 (144.75-253.75)	<0.001**
PPBS (mg/dL)	101.50 (94.25-117.25)	183.50 (124.75-237.50)	271 (187.50-313.25)	<0.001**
HbA1c (%)	5 (4.9-5.4)	6.95 (6.225- 7.975)	9.30 (7.95- 10.35)	<0.001**

Based on the normality of the variable, data is represented as Mean ± standard deviation (SD) or Median with Interquartile (IQR). Comparison done via ANOVA or Kruskal Wallis as the test of significance as applicable; * p <0.05Statistically significant; ** p <0.001Statistically significant; FBS – Fasting blood sugar; PPBS – Postprandial blood sugar; HbA1c – Glycated hemoglobin

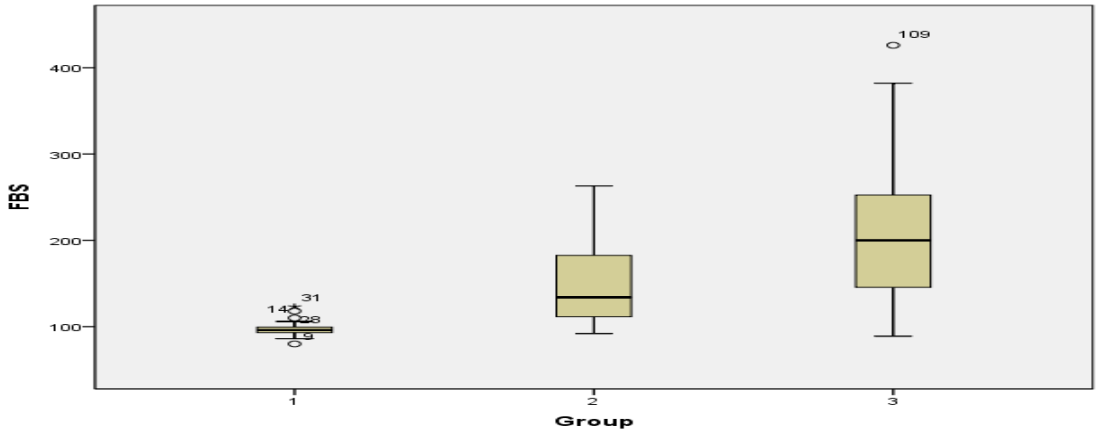

Fig. 1: Box-whiskers plot comparing fasting blood sugar between Group I(low-risk), Group II (intermediate-risk), and Group III (high-risk)

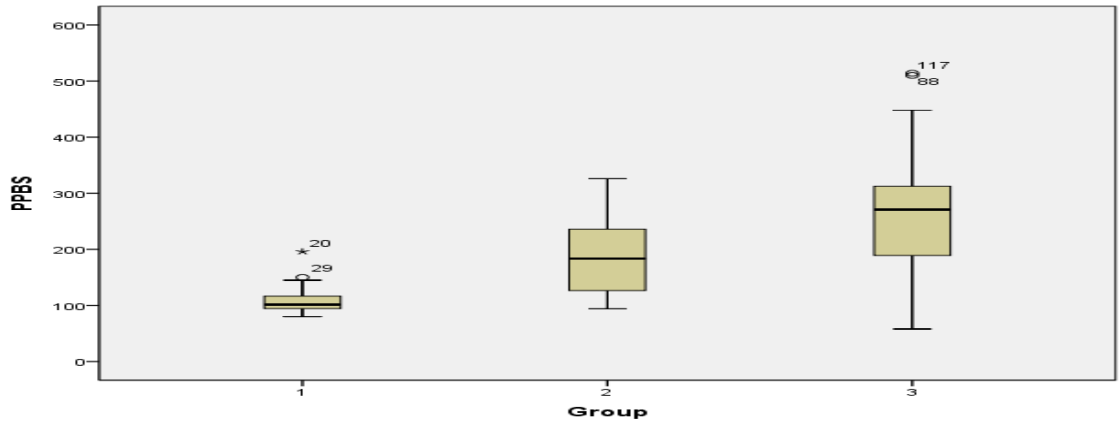

Fig. 2: Box-whiskers plot comparing postprandial blood sugar between Group I(low-risk), Group II (intermediate-risk), and Group III (high-risk)

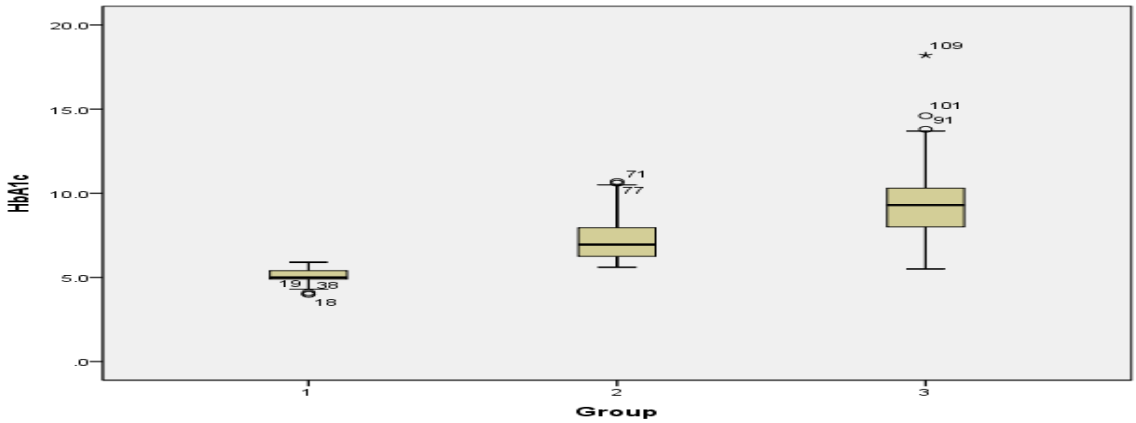

Fig. 3: Box-whiskers plot comparing glycated hemoglobin between Group I(low-risk), Group II (intermediate-risk), and Group III (high-risk)

Table 5: Correlation analysis of age, blood glucose level (both fasting and postprandial), and HbA1c with hs-CRP

Correlation coefficient (R-value) with hs-CRP		***p* value**
Age	1.000	0.77
TLC	0.344	<0.001**
ESR	0.173	0.058
FBS	0.788	<0.001**
PPBS	0.743	<0.001**
HbA1c	0.873	<0.001**

Spearman correlation was done. Correlation coefficient expressed as R-value'; *Statistically significant p <0.05; **Statistically significant p <0.001; ESR- Erythrocyte sedimentation rate; FBS – Fasting blood sugar; PPBS – Postprandial blood sugar; HbA1c – Glycated hemoglobin; TLC-Total leukocyte count

Table 6: Correlation analysis of total leukocyte count with glycated hemoglobin

Correlation coefficient (R-value) with HbA1c		***p* value**
TLC	0.281	<0.001**

Spearman correlation was done. Correlation coefficient expressed as R-value; *Statistically significant p <0.05; **Statistically significant p <0.001; HbA1c – Glycated hemoglobin; TLC – Total leukocyte count

DISCUSSION

This was a retrospective study conducted at a tertiary care hospital, Tamil Nadu. The study consisted of 120 participants who attended the Master health check-up at our hospital. The study participants were grouped into three groups based on their hs-CRP levels.

There was no significant difference in age among the three groups. Also, we could not obtain any significant correlation between age and the levels of hs-CRP in our study. Hence, age is not a confounding factor in this study.

The total leukocyte count is defined as the sum-total of all types of white-blood-cell namely, neutrophils, lymphocytes, monocytes, and eosinophils. Total leukocyte count depends on various factors like age, gender, environmental factors, genetic inheritance, diet, and lifestyle.

The total leukocyte count > 11000 cells/cmm is known as leukocytosis. Leukocytosis is a nonspecific marker of inflammation resulting from acute or chronic infection, malignancy, trauma, allergies, etc (14). In our study, the total leukocyte count showed a statistically significant increase across the groups, though the total leukocyte count was within the normal limits. Also, the total leukocyte count had a significant positive correlation with hs-CRP. As the hs-CRP levels increased the total leukocyte count also increased.

Increased leukocyte count within the normal range signals the elevated ongoing systemic inflammation. Lee *et al.,* in a prospective study, had shown that elevated WBC count within the normal range is associated with an escalated incidence of ischemic heart disease and also mortality from cardiovascular diseases (15).

The total leukocyte count had a significant positive association with glycated hemoglobin in this study. Glycated hemoglobin > 6.5% is diagnostic of diabetes mellitus. Diabetes mellitus is characterised by elevated mediators of inflammation which inhibit insulin receptor signal transduction by stimulating phosphorylation of serine residues of IRS-1. This prevents IRS-1 from associating with insulin receptors resulting in insulin resistance (16).

The Erythrocyte sedimentation rate measures the rate (mm/h) at which red blood cells form aggregates (or rouleaux) that sediment when anticoagulated fresh blood is left in a vertical tube'. It is a marker of non-specific inflammation. In this study, all the participants had ESR within the normal limits, but it showed a statistically significant increase across the groups. In this study, we could not obtain a statistically significant correlation between ESR and hs-CRP. Erikssen *et al.,* in a follow-up study conducted over 7 years has demonstrated that ESR is a reliable predictor of cardiovascular diseases even in apparently healthy adults (17).

On comparing fasting blood glucose, postprandial blood glucose, and HbA1c, there was a significant difference among the groups. There was a statistically significant positive correlation. So, when hs-CRP levels increased, the fasting blood sugar, postprandial blood sugar, and HbA1c also increased.

The median fasting blood glucose in group 1 with hs-CRP level < 1 mg/ml was 96 mg/dL. Hence, individuals with low cardiovascular risk had normal fasting blood sugar. In the group with intermediate cardiovascular risk, the fasting blood sugar was 134 mg/dL, which is in the diabetes mellitus range. In the group with increased cardiovascular risk, the median fasting blood sugar was 200 mg/dL.

This finding was in agreement with the previous studies. Park *et al.,* in their prospective cohort study in which 1,197,384 Korean adults were followed up for 16 years, fasting blood sugar showed a statistically significant association with cardiovascular disease incidence and mortality. They also showed that at fasting blood sugar levels >100 mg/dL, the risks of cardiovascular risk progressively increased (18). A prospective cohort study conducted by Lee *et al.,* in which 2,27,938 subjects were followed up for 17 years showed that fasting glucose levels between 95-124 mg/dL were associated with the least cardiovascular events (19). Hence, impaired fasting blood sugar may predict the risk of cardiovascular disease in the future. Also, stringent control of fasting blood sugar is beneficial for the patient by decreasing the long-term risk of developing cardiovascular disease.

The median postprandial blood sugar in the group with low cardiovascular risk was 101.50 mg/dL, in the group with average risk was 183.50 mg/dL and in the group with high risk for cardiovascular events is 271 mg/dL. Post-prandial blood sugar and hs-CRP had a significant positive correlation. As the post-prandial blood sugar increased, the risk for adverse cardiovascular events also increased. This result is consistent with already published studies. Donahue *et al.,* in their follow-up study conducted over 12 years on 6394 non-diabetic men had shown a continuously increasing risk gradient between postprandial blood glucose and cardiovascular risk (20).

Lin *et al.,* have shown that postprandial blood sugar will improve the ability to identify non-diabetic

individuals who are at increased risk of developing cardiovascular disease in the future (21). The post-prandial blood glucose creates a situation where many risk factors of cardiovascular disease converge. Elevated postprandial blood sugar mirrors the increased concentration of lipid, predisposing to atherosclerosis. The postprandial phase changes the inflammatory milieu by increasing the levels of tumour necrosis factor-α and interleukin-6 (22). This will in turn increase the synthesis and release of CRP from the liver. Also, the postprandial hyperglycemia results in increased production of free radicals resulting in endothelial dysfunction; a proinflammatory event.

The HbA1c level in the low-risk group was 5%. The interquartile range was between 4.9 and 5.4, which is a normal range of HbA1c. But the HbA1c level in the intermediate-risk (group II) and high-risk (group III) was in the pre-diabetic and diabetes mellitus range. HbA1c and hs-CRP also showed a significant positive correlation in the current study. Hence, HbA1c level in the pre-diabetic and diabetic range is associated with an elevated risk of adverse cardiovascular events.

Cavero-Rodendo *et al.*, in their meta-analysis have shown that HbA1c level > 8% in diabetes mellitus patients were associated with a significant increase in cardiovascular mortality (23). AHA has recommended measurement of HbA1c for cardiovascular risk assessment in asymptomatic adults without a diagnosis of type 2 diabetes mellitus (24).

The hyperglycemia and insulin resistance associated with diabetes mellitus results in increased oxidative stress and activation of protein kinase C and receptors of advanced glycation end-products. This leads to an increase in endothelin-1, angiotensin II, NF-Kb, activator protein-1, tissue factor, prostacyclin and plasminogen activator-1, and down-regulation of nitric oxide in the endothelium. All these changes result in vasoconstriction, inflammation and thrombosis. Thrombosis occurs as a result of hypercoagulation, platelet activation, and decreased fibrinolysis. All these factors converge to the development of atherosclerosis (25).

Hence, this study shows that impaired glycemic control is associated with an increased risk of an adverse cardiovascular event. The primary pathological mechanism that increases cardiovascular risk is atherosclerosis. Atherosclerosis is a chronic inflammatory condition that results in an increased concentration of hs-CRP in the circulation. Also, our study has several limitations. First, it is a retrospective study. Second, the sample size was relatively small. Third, the relationship of hs-CRP with lipid indices was not analysed.

CONCLUSION

The study aimed to correlate the levels of serum high-sensitivity C-reactive protein (hs-CRP) with glycated hemoglobin (HbA1c). From this current study, we could conclude that hs-CRP has a significant association with HbA1c. Also, fasting blood sugar and postprandial blood sugar had a strong positive correlation with hs-CRP. Additionally, we also observed that total leukocyte count had a significant positive correlation with hs-CRP and HbA1c. Hence, our results show that impaired glycemic control is associated with an increased risk of developing cardiovascular diseases.

CONFLICT OF INTEREST

No conflicts of interest.

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