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# Correlation between hs-CRP, HbA1c and Oxidative Stress in Type-2 Diabetic Patients.

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## Abstract

**Background:** Diabetes mellitus is a collection of common metabolic disorder mainly considered by hyperglycaemia which results commencing from defective insulin secretion or insulin action or both. **Subjects and Methods:** 50 Type 2 Diabetic patients and 50 non diabetic subjects between the age group of 30-65 years who were all attending in OPD at Santosh Medical college and Hospital Ghaziabad, were selected for the study. All the patients were included as cases evaluated and diagnosed as Type 2 Diabetes mellitus on the basis of history and Biochemical investigations. **Results:** Significant positive correlation with a p value <0.000 was found between fasting blood glucose (FBS), postprandial blood glucose (PPBS) and hs-CRP level. Similarly, statistically significant positive correlation (p value<0.000) was also found between Glycosylated hemoglobin (HbA1c) and hs-CRP in the study group. **Conclusion:** There is strong association found between fasting & postprandial serum glucose, high-sensitivity C-reactive protein and glycated haemoglobin, MDA & Thiols.

**Keywords:** High sensitivity C reactive protein (hs-CRP), MDA &Thiols.

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## Introduction

Diabetes mellitus is a collection of common metabolic disorder mainly considered by hyperglycaemia which results commencing from defective insulin secretion or insulin action or both.[1] Diabetes mellitus is considered to be a state of persistent low grade inflammation which contributes to the pathogenesis of disease.[2] Inflammation is a state of local protective response to tissue injury.[3] In addition to local response, systemic response called as acute-phase response is depicted by the changes in levels of acute phase reactants like C-Reactive Protein(CRP), complement system proteins, serum amyloid A, haptoglobin and fibrinogen.[4] Patients with diabetes mellitus aggravate other co-morbidities like hypertension, obesity and dyslipidemia which in turn increase the risk for Cardio Vascular Disease (CVD).[5]

C reactive protein, measured as high sensitivity C reactive protein (hsCRP), an acute phase protein is produced by the liver and their levels increase whenever there is instances of inflammation in the body.[6] CRP may also rise in acute Coronary Syndrome, arthritis, autoimmune disease, inflammatory bowel disease, pancreatitis, colitis and carcinoma. CRP testing cannot be used to diagnose specific diseases but serves more as a general indicator of inflammation or infection.[7] Numerous epidemiologic studies done in United States and Europe have concluded high-sensitivity C-reactive protein (hs-CRP) to be a predictor of future coronary events among apparently healthy individuals.[8] CRP has received the most attention as a marker of inflammation in both rheumatic and non-rheumatic disease. CRP can rise as high as 1,000-fold with inflammation. Conditions that commonly lead to marked changes in CRP include infection, trauma, surgery, burns, inflammatory conditions, and advanced cancer. Moderate changes occur after strenuous exercise, heatstroke, and childbirth. Small changes occur after psychological stress and in several psychiatric illnesses.

Increased oxidative stress plays a major role in the progression of diabetes and development of complications.[9] Oxidative stress increases when the rate of free radical production is increased and/or the antioxidant mechanisms are impaired.[10] Free radicals are unstable species which are produced continuously during aerobic metabolism. These free radicals cause oxidative damage to carbohydrates, proteins, lipids and DNA that are normally neutralized by protective antioxidants. The imbalance between increased free radical production and protective antioxidants to neutralize it, leading to oxidative damage is known as oxidative stress. Oxidation of glucose and glycosylated proteins in type 2 diabetic patients is thought to be the reason for increased production of damaging free radicals.[11]

Aim of this present study was to assess the Correlation Between hs-CRP, HbA1c and Oxidative Stress in Type-2

Diabetic Patients.

## Subjects and Methods

This present study was conducted in the Department of Biochemistry, Santosh Medical College and Hospital, Ghaziabad. 50 Type 2 Diabetic patients and 50 non diabetic subjects between the age group of 30-65 years who were all attending in OPD at Santosh Medical College and Hospital Ghaziabad, were selected for the study. All the patients were included as cases evaluated and diagnosed as Type 2 Diabetes mellitus on the basis of history and Biochemical investigations during the period July-2017 to August-2018 according to inclusion and exclusion criteria. The study was approved by Santosh Medical College and Hospital, Ghaziabad. Informed consent was obtained from all the participants.

**Biochemical Investigation:**

5ml of fasting venous blood samples were collected in clot activator coated polypropylene tubes by vein puncture under strict aseptic precaution as soon as the subjects got admitted as per the inclusion criteria. Similar way 2 hours post prandial also collected. Blood samples were centrifuged at 3000 rpm used for 10 minutes and serum was separated. 8-12 hours fasting samples, 2 hours post prandial samples were collected from all subjects during their hospital visit and analysis of below said parameters were done. (Fasting and Post prandial blood glucose, Glycated Hemoglobin (HbA1c), Fasting Serum Lipid parameters which include (Total cholesterol, Triglycerides, LDL-cholesterol, HDL- cholesterol), Serum high sensitivity C-reactive protein (hs-CRP), Serum Malondialdehyde(MDA) and Plasma protein Thiols.

**Statistical Analysis**

All the data was initially entered to Microsoft Excel 2010 and later these spreadsheets were used for analysis. Statistical analysis was done by using SPSS version 20.0. We used student t-test and pearson's correlation coefficient to find the statistical significance. A P-value <0.05 was to be considered statistically significant.

## Results & Discussion

**Table 1: Distribution of gender in the study group and control group.**

| Sex | Control group | | Study group | |
|---|---|---|---|---|
| | Number(n= 50) | Percentage( %) | Number(n= 50) | Percentage( %) |
| Male | 29 | 58.0 | 27 | 54.0 |
| Female | 21 | 42.0 | 23 | 46.0 |
| Total | 50 | 100 | 50 | 100 |

This present study conducted in the Department of Biochemistry, Santosh Medical College and Hospital, Ghaziabad. 50 type 2 diabetic patients which included 27 males and 23 females. Similarly, the control group also had 50 (29 males and 21 females) Non diabetic subjects. [Table1]

**High Sensitivity C-Reactive Protein (hs-CRP):**

**Table 2: Mean concentration of hs-CRP in Study group and control group:**

| Variables | | Mean ± SD | P-value |
|---|---|---|---|
| hsCRP (mg/L) | Cases | 3.43 ± 1.14 | < 0.0001 |
| | Controls | 2.32 ± 0.63 | |

[Table2 &Figure 1] The mean hsCRP level in type 2 DM subjects was 3.43 mg/L and standard deviation is 1.14 mg/L. In the control group, the value was 2.32 mg/L and standard deviation is 0.63 mg/L. For 42 diabetic patients, hsCRP was > 3.0 mg/dL (high risk).

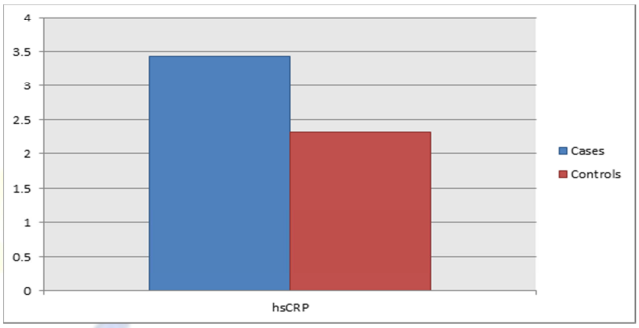


**Figure 1: Mean concentration of hs-CRP in cases and controls group.**

**Malondialdehyde (MDA):**

**Table 3: Mean concentration of MDA in Study group and control group**

| Variables | | Mean ± SD | P-value |
|---|---|---|---|
| MDA (nmol/ml) | Cases | 2.93 ± 0.56 | < 0.0001 |
| | Controls | 1.66 ± 0.35 | |

[Table3 & Figure 2] The mean MDA level in type 2 DM subjects was 2.93 nmol/ml and standard deviation is 0.56 nmol/ml. In the control group, the value was 1.66 nmol/ml and standard deviation is 0.35 nmol/ml.


**Figure 2: Mean concentration of MDA in Study group and control group**

**Plasma Protein Thoils:**

**Table 4: Mean concentration of Thiols in Study group and control group:**

| Variables | | Mean ± SD | P-value |
|---|---|---|---|
| Thiols (µmol/L) | Cases | 542.78 ± 155.09 | < 0.0001 |
| | Controls | 705.32 ± 159.50 | |

[Table4 & Figure 3] The mean Thiols level in type 2 DM subjects was 542.78 µmol/L and standard deviation is 155.09 µmol/L. In the control group, the value was 705.32 µmol/L and standard deviation is 159.50 µmol/L.

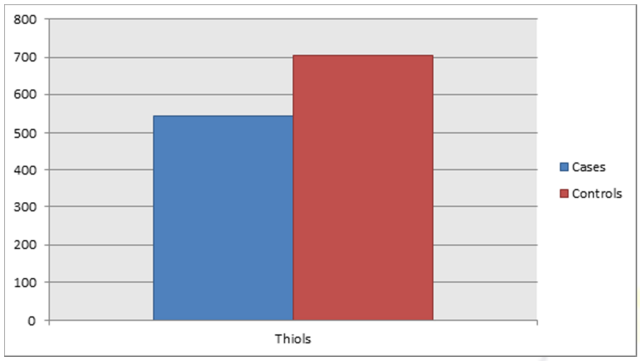


**Figure 3: Mean concentration of MDA in Study group and control group**

**Table 5: Correlation between age, BMI and hs-CRP in the study group**

| Variables | N | Pearson Correlation('r') |
|---|---|---|
| Age | 50 | - 0.102 |
| BMI | 50 | + 0.011 |

[Table5] shows the statistically not significant negative correlation (p value <0.48) was found between age of the subject and hs-CRP level. Similarly, statistically not significant positive correlation (p value <0.93) was found between Body Mass Index and hs-CRP.

**Table 6: Correlation between FBS, PPBS, HbA1c and hs-CRP in the study group**

| Variables | N | Pearson Correlation('r') |
|---|---|---|
| FBS | 50 | + 0.843 |
| PPBS | 50 | +0.806 |
| HbA1c | 50 | +0.920 |

**Table 7: Correlation between lipid profile and hs-CRP in the study group:**

| Variables | N | Pearson Correlation('r') |
|---|---|---|
| Total Cholesterol | 50 | +0.659 |
| Triglycerides | 50 | +0.623 |
| High Density Lipoprotein Cholesterol | 50 | -0.764 |
| Low Density Lipoprotein Cholesterol | 50 | +0.699 |

[Table6] Shows the statistically significant positive correlation with a p value <0.000 was found between fasting blood glucose (FBS), postprandial blood glucose (PPBS) and hs-CRP level. Similarly, statistically significant positive correlation (p value<0.000) was also found between Glycosylated hemoglobin (HbA1C) and hs-CRP in the study group.

[Table7] Shows the statistically significant positive correlation with a p value of <0.000 was found between serum total cholesterol, triglycerides and low density lipoprotein cholesterol and hs-CRP level. There was no statistically significant negative correlation between high density lipoprotein cholesterol and hs-CRP.

**Table 8: Correlation between MDA, Thiols and hs-CRP in the study group**

| Variables | N | Pearson Correlation('r') |
|---|---|---|
| MDA | 50 | +0.947 |
| Thiols | 50 | +0.292 |

[Table 8] Shows the statistically significant positive correlation (p value 0.000) was found between MDA and hs-CRP. There were significant correlation between MDA of the subjects and hs-CRP level.

Similarly, a statistically significant positive correlation (p value 0.03) was found between Thiols and hs-CRP. There was significant correlation between Thiols of the subjects and hs-CRP level.

**Blood sugar**

The mean ± SDs of fasting and postprandial serum glucose in controls and type 2 diabetic subjects were in the range of 83.16 ± 7.65 mg/dL and 139.84 ± 16.82 mg/dL, and 115.9 ± 8.32 mg/dL and 223.36 ± 30.43 mg/dL respectively. The mean value of fasting and postprandial serum glucose was higher in type 2 diabetic subjects compared to controls. The increase is found to be statistically highly significant (p <0.0001) which is in accordance with Amanullah S et al,[12] Mahajan A et al &Meshram A et al.[13,14]

Hyperglycemia in DM is caused by both overproduction and underutilization of glucose. There is a relative excess of glucagon also. As a consequence, glucose production is increased rather than consumption by liver, and also there is drastic reduction of uptake of glucose into muscle and adipose tissue finally contributing to hyperglycemia.[15]

**Lipid**

The association between dyslipidemia and diabetes mellitus is well established. Although various lipoprotein abnormalitics havc bccn dcscribcd in paticnts with diabctcs mellitus. The results of the present study showed significantly increased levels of total cholesterol (p= 0.0001) and LDL-C (p= 0.0001) and high TG (p= 0.0001) whereas HDL-C (p= 0.0001) was decreased among diabetic subjects compared to controls. These findings are in good agreement with others studies (Smaoui et al.,2004,[16]Garg and Grundy, 1990,[17]Dazien et al., 1991,[18] Howard, 1978.[19] Diabetic dyslipdemia is well known in various studies including the Heart Protection Study,[20] Anglo-Scandinavian Cardiac Outcomes Trial-Lipid-Lowering Arm,[21] the Collaborative Atorvastatin Diabetes Study,[22] the Lescol Intervention Prevention Study,[23] and the Cholesterol and Recurrent Events study.

**High-sensitivity C-reactive protein**

The mean ± SD of hs-CRP in controls and type 2 diabetic subjects were in the range of 2.32 ± 0.63 mg/L and 3.43 ± 1.14 mg/L, respectively. The mean value of hs-CRP in type 2 diabetic subjects was higher when compared to controls.

The increase was found to be statistically highly significant ($p < 0.0001$). This is in accordance with Ridkar M.P,[24] Chamber J.C et al,[25]Coban E,[26]Yaun G et al,[27]Yorulmaz E & Schulze M.B et al.[28,29]

It was also observed that hs-CRP levels positively correlated with FBS, PPBS, HbA1c, Tc, TG and LDL which is in accordance with Nakanishi N et al,[30] Wu T et al,[31] King D.E et al,[32] and Mahajan A et al.[13]

High sensitivity C-reactive protein is an acute phase reactant produced by liver, is an extremely sensitive biomarker of systemic inflammation. It is perceived that chronic low-grade inflammation as evidenced by elevated high-sensitivity C-reactive protein might potentially be a cause underlying the etiology and manifestation of type 2 diabetes although the exact mechanisms are still not well understood. Additionally, hs-CRP has also emerged as a powerful predictor of cardiovascular disease.

Some investigators hypothesized that decreased insulin sensitivity may lead to enhanced CRP expression by counteracting the physiological effect of insulin on hepatic acute-phase protein synthesis. Clamp studies in normal subjects showed that insulin exerts selective effects on hepatic protein synthesis, reducing the expression of acute-phase response proteins. Resistance to this effect would in turn lead to increased synthesis of acute-phase proteins such as CRP. Large prospective studies pointed out the involvement of increased hs-CRP on cardiovascular morbidity and mortality. High levels of hs-CRP have been shown to be an independent predictor of cardiovascular risk for all degrees of severity of metabolic syndrome and type 2 diabetes.[33]

In hyperglycemic condition the concentration of advanced glycation end products is elevated that has been shown to activate macrophages, increase oxidative stress and upregulate synthesis of interleukin-1 (IL-1), IL-6 and tumour necrosis factor (TNF-α) resulting in production of CRP.[30]

IL-1 family members are proinflammatory cytokines that initiate the innate immune response by activating a set of transcription factors including nuclear factor kappa B (NF-kB) and activator protein 1 (AP-1). Both apoptotic cells producing IL-1 and IL-18 as well as activated cells can release these cytokines into local milieu but this appears to be associated with caspase-1 activation. This further leads to IL-1 associated inflammation in type 2 diabetes mellitus.[34]

IL-6 increases postprandially, in parallel to glucose and insulin concentrations in interstitial fluid of subcutaneous adipose tissue. TNF-α produce insulin resistance by influencing the function of insulin receptor and inhibiting insulin secretion. Because adipose tissue produces IL-6 and TNF-α and the synthesis of CRP, mostly under the control of IL-6 and TNF-α, stimulates the production of CRP.[30]

**Glycated Hemoglobin:**

The mean ± SDs of HbA1c in controls & type 2 diabetes were in the range of 4.91 ± 0.33 & 7.95 ± 0.84 % respectively. The mean value of HbA1c was higher in type 2 diabetic subjects as compared to controls. The increase was statistically highly significant ($p < 0.0001$). This is in accordance with Shetty J.K,[35]Sathiyapriya V et al,[36] Yan R et al,[37]Dalan R et al,[38]& Singer D.E et al.[39]

It was also observed that HbA1c level positively correlated with hs-CRP. This is in accordance with Meshram A et al,[14] Shetty J.K et al,[35]& Sultan S et al.[40]

Glycated hemoglobin concentration represents the integrated values of glucose over preceding 6 to 8 weeks since the rate of formation of HbA1c is directly proportional to the concentration of glucose in blood.

It is currently considered as the best index of metabolic control for diabetic patients in clinical setting. It is as well a measure of risk for the development of micro and macrovascular complications.[41,42]

The most important factor governing the quantity of glycated hemoglobin formed is the prevailing plasma glucose concentration. As the plasma glucose concentration is increased in diabetic subjects, glycated hemoglobin also increased in diabetic subjects.[43]

Glycated hemoglobin levels probably reflect the degree of glycemic control of the individual better than measuring fasting and post-prandial blood glucose levels. This is because glycated hemoglobin does not depend on variables such as patient co-operation, time of the day, stress, exercise, food intake or renal threshold. This makes attractive screening test in population studies.[44]

It represents the mean daily blood sugar concentration and degree of carbohydrate imbalance, better than fasting blood glucose concentrations or glucose tolerance test results. Hence it may provide a better index of control of diabetic patient without resorting to a glucose loading procedure.[45]

Type 2 diabetic Patients have higher malondialdehyde (MDA) and lower total plasma protein thiol levels than the controls; MDA and total thiols represent the oxidative damage products of lipids and proteins respectively.[46]Jaiprakash et al have studied the plasma thiol levels in three groups namely control, diabetic patients per se and diabetic people with end stage renal disease (ESRD). The results showed that plasma thiol concentration was significantly decreased in diabetic patients without ESRD when compared with controls.[47,48]There was also a significant rise in plasma thiols in diabetic patients with end stage renal disease when compared to controls which concurred with other studies.[49,50]

Rama Srivatsan et al also have studied protein thiol levels in three groups namely controls, diabetic and diabetic people with microvascular complications. According to that study there was no significant difference in protein thiol concentration between control and type 2 diabetics and also with type 2 DM with complications (P=0.79,P=0.55).[51]

Another study has correlated hsCRP with HbA1c levels in overweight type 2 diabetic female patients.[52]Bahceci M et al analysed high sensitivity CRP levels in Type 2 diabetic

men without coronary heart disease, non-diabetic CHD patients and T2DM patients with CHD. He also concluded that there is a positive correlation between serum hs-CRP and HbA1c levels. Finding of this current study also substantiates the results of previous studies. Pearson correlation shows a positive correlation between glycatedhaemoglobin (HbA1c) levels and hs-CRP with r value 0.216.p value is found to be 0.018 which is statistically significant.

Previous studies have shown that measurement of intracellular and extracellular aminothiol compounds will describe the effect of oxidative stress in the body.[53]According to a study by Salman Ashfaq measurement of thiols which determines the oxidative stress predicts early atherosclerosis, which is measured by carotid intima- media thickness.[54] The current study and the analysis of the results suggests a very significant positive correlation between the hsCRP levels in plasma and the plasma total protein thiols in all the subjects who have diabetes with or without complications of diabetes with p value of < 0.001. This is suggestive of the fact that inflammatory status and oxidative stress are proven concepts behind pathogenesis of diabetes, a chronic disease of mankind. hsCRP is an established marker of inflammation and infections while change in thiol levels are noted in many studies involving stress induced due to oxidative changes because of persistent hyperglycemia. One study has shown that poor glycemic control due to persistent hyperglycemia causes glycation of proteins leading to increased oxidative damage of proteins and this increases the rate of development of diabetes related complications.[55] HbA1c level in the blood is not only a direct predictor of the risk of complications in diabetes, but also a prognostic marker and treatment guide for Diabetes and hence the results are suggestive of the fact that as HbA1c levels rise, the severity of complications also rise which indirectly suggests the inflammatory status /oxidative stress state is prevalent in the patients under study. Change in thiol levels are noted in many studies due to oxdative stress resulting from persistent hyperglycemia. In this current study the change in thiols is in the upward direction which facilitates the idea of induction in the synthesis of thiols to counter the oxidants. Some studies on the other hand have shown a fall in thiol levels due to oxidative damage which has been explained by consumption and near exhaustion of thiols in the process of neutralizing the oxidant radicals.[56]

## Conclusion

In conclusion, there is significant elevation in the levels of FBS, PPBS, HbA1c, Total Cholesterol, Triglyceride, LDL-C, MDA, CRP, whereas HDL-C, Thiols, were decreased among Type 2 Diabetic Patients compared to healthy controls. There is strong association found between fasting & postprandial serum glucose, high-sensitivity C-reactive protein and glycatedhaemoglobin, MDA &Thiols. According to our results together with previous other studies findings, we suggest that the quantitative determination of high-sensitivity C-reactive protein, MDA &Thiols help in predicting type 2 diabetes mellitus associated cardiovascular complications. Glycated hemoglobin provides a retrospective index of glucose control over a time in Diabetic subjects. Measurement of glycated hemoglobin serves as a simple and rapid procedure to assess glycemic control. It serves both as a screening test for control of diabetes and as an indicator of efficacy of treatment. Thus the study concluded that inflammatory biomarkers like high-sensitivity C-reactive protein, MDA and Thiols are strongly and independently associated with cardiovascular complications in diabetes. In addition regular exercises and effective administration of anti-inflammatory agents may offer protection against type 2 diabetes mellitus associated complications.

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