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Study of Serum High-Sensitivity C-Reactive Protein, Ferritin and Glycated Hemoglobin Levels in Patients with Type 2 Diabetes Mellitus

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Abstract: ***Introduction: Systemic inflammatory activity plays a key role in the pathogenesis and progression of atherosclerosis in subjects with type 2 diabetes. Hence evaluation of inflammatory novel biomarkers like high-sensitivity C-reactive protein and ferritin serves as tools for cardiovascular risk prediction. Objectives: to evaluate the levels of high-sensitivity C-reactive protein (hs-CRP), ferritin& glycated haemoglobin in controls and type 2 diabetic subjects and to assess the correlations if any, between fasting serum glucose, hs-CRP, ferritin& glycated haemoglobin. Materials and Methods: A total number of 100 subjects were studied, comprising of 50 controls and 50 type 2 diabetic subjects. Diabetic subjects were further divided depending upon treatment modalities. Serum levels of hs-CRP, ferritin were measured by Chemiluminescense Immunoassay. Glycated haemoglobin was measured by Nephelometry. The statistical analysis was carried out using student't' test and Karl Pearson's coefficient of correlation. Results: hs-CRP, ferritin & glycated haemoglobin levels were found to be significantly increased (p<0.01) in type 2 diabetic subjects compared to controls. There was highly significant (P<0.01) positive correlations existed between fasting serum glucose, hs-CRP and HbA1c. Discussion & Conclusion: Elevated levels of hs-CRP and ferritin predict the future cardiovascular complications in type 2 diabetic subjects. Glycated haemoglobin serves as a simple and rapid biomarker to assess glycemic control in type 2 diabetic subjects. The current study demonstrates that higher HbA1c levels are significantly associated with elevation of hs-CRP. These results imply a significant relation between glycemic control, inflammation and cardiovascular risk.***

Keywords: Type 2 Diabetes Mellitus, Glycated haemoglobin, High-sensitivity C-reactive protein & Ferritin

1. Introduction

Diabetes Mellitus, a Dysglycemic Metabolic Syndrome refers to a group of common metabolic disorders that share phenotype of hyperglycemia, due to reduced insulin secretion, decreased glucose utilization and increased glucose production.[1] The Hindu physicians Sushrutha and Charaka wrote between 400-500 BC were probably first to recognize sweetness of Diabetic urine. Indeed the diagnosis was made by tasting the urine or noting that ants congregated round it. They noted that the disease was most prevalent in those who were indolent, overweight and gluttonous who indulged in sweet and fatty foods.[2]

The prevalence of Diabetes has shown increasing trend in the last three decades in India. Currently the total number of people with Diabetes India is 61.3 million and is expected to increase to 101.2 million by 2030.[3]

Systemic inflammatory activity plays a key role in the pathogenesis of vascular atherosclerosis, insulin resistance and type 2 diabetes mellitus. Inflammatory biomarkers may therefore be a valuable tool for risk evaluation. Among them, the best evidence to date supports the use of hs-CRP as an independent predictor of increased cardiovascular disease risk in diabetic and non diabetic subjects. C-reactive protein is an acute phase protein synthesized by the liver found in circulation in response to low grade inflammationand plasma levels of hs-CRP provide a sensitive marker of an increased inflammatory activity in the arterial wall.[4]

Ferritin is a storage form of iron found in nearly all the cells of the body. The increased levels of ferritin in the blood reflect both the involvement of inflammation and independent actions of excess iron. It is known that increased accumulation of iron affects insulin synthesis and secretion in the pancreas and interferes with insulin-extracting capacity of the liver leading to hyperinsulinemia, impaired insulin secretion, insulin resistance and diabetes.[5]

In 1976, the HbA1c (Glycated hemoglobin), test was introduced as a monitor of glycemic control. Glycated hemoglobin is formed when aldehyde group of glucose and some other hexoses combine irreversibly, post-translationally, non-enzymatically with N-terminal valine residues of each β-chain of hemoglobin and this process is substrate concentration dependent Measurement of HbA1c is considered as gold standard for monitoring chronic glycemia in Diabetic patients. Hence monitoring glycemic status has been considered as cornerstone of diabetic control.[6]

2. Objectives

1) To evaluate high sensitivity C-reactive protein, ferritin & glycated hemoglobin levels in type 2 diabetic subjects & controls
2) To determine the correlations if any, between fasting serum glucose, high-sensitivity C-reactive protein, ferritin & glycated hemoglobinin type 2 diabetic subjects.

3. Materials and Methods

a) Source of data

A case-control study of hs-CRP, ferritin and HbA_{1c} was conducted in age and sex matched type 2 diabetic subjects and controls from S. S Hospital, Davangere (attached teaching hospital of S.S Institute of Medical Sciences &

Research Centre, Davangere) between May 2012- April 2013.

The study was approved by the ethical and research committee of S.S Institute of Medical Sciences and Research Centre, Davangere, to use human subjects in the research study. Written informed consent was taken from the study subjects.

Type 2 Diabetic subjects and controls participated voluntarily in the study. Detailed medical history and relevant clinical examinations were carried out in both cases and controls. Based on inclusion and exclusion criteria, about 50 cases of type 2 diabetic subjects and 50 age and sex matched healthy controls were included.

b) Inclusion Criteria:

Cases: 50 proven cases of type 2 diabetic subjects in the age group of 30-55 years.All the patients suffering from type 2 diabetes since 8 or < 8 years diagnosed and confirmed according to World Health Organization criteria (FBS ≥126 mg/dl &2 hour plasma glucose ≥ 200 mg/dl during an OGTT).Patients on treatment with oral antidiabetic medications (only on sulfonylureas) and those on insulin treatment were included.

Controls: An equal number of healthy controls age and sex matched as that of cases were included.

c) Exclusion criteria

a. Type 1 diabetic subjects.
b. Children & adolescents.
c. History of myocardial infarction and angina which are known to influence serum levels of hs-CRP
d. History of liver, kidney, acute illness and thyroid diseases, anemia, haemochromatosis which are known to influence the serum levels of Ferritin and hs-CRP
e. Gestational Diabetes Mellitus
f. Patients on metformin & statins therapy which are known to influence serum hs-CRP levels
g. Women on hormone replacement therapy which are known to influence serum hs-CRP levels

d) Method of sample collection:

Type 2 diabetic subjects who were on insulin treatment were instructed not to take insulin for 2 days prior to the collection of fasting venous sample.

Under aseptic precautions about 6 mL of fasting venous blood was drawn from ante-cubital vein of study subjects using a sterile disposable syringe. Of that, 4 mL was collected in plain vacutainer and 2 mL into EDTA containing vacutainer. Plain vacutainer containing 4 mL of blood was subjected for centrifugation and the serum was separated. The biochemical parameters were analyzed by Chemiluminescense immunoassay and Nephelometry.

e) Parameters measured:

In the present study following parameters were estimated.

I. Serum was used for the estimation of following parameters

1) Fasting serum glucose,
2) High Sensitivity C-reactive protein,
3) Ferritin,

II. Whole blood was used for the estimation of Glycated hemoglobin

Based on inclusion and exclusion criteria, age and sex matched controls and cases are included in the present study after obtaining informed consent. A proforma was used to record relevant information and patient's data. Serum concentration of glucose was estimated by glucose oxidase method[7]using analytical kits from Erba Diagnostics Mannheim GmbH in semi-autoanaylzer (CHEM-5 Plus V_2, Erba Mannheim). Serum concentrations of hs-CRP, ferritin were estimated by Chemiluminescense immunoassay[8,9] (CLIA) kits from Acculite Monobind in Lumax CLIA strip reader.Glycated hemoglobin was estimated by Nephelometry[10] kits from Agappe in MISPA-i card reader.

f) Statistical Analysis

Mean and standard deviations were used to describe the data. Students't' test was used for comparison between controls and study subjects. Relationship between variables was assessed by Karl Pearson's coefficient of correlation. P-value of 0.05 or less was considered as statistically significant.

1. Arithmetic mean $= \frac{\text{Sum of all the values}}{\text{No. of values}} = \frac{\sum X}{n}$

2. Standard deviation, $SD = \sqrt{\frac{\sum (X - \bar{X})^2}{n-1}}$

3. Student's unpaired't' test

$$T = \frac{\text{Difference of means}}{\text{S.E of difference of means}}$$

4. Karl Pearson's coefficient of correlation

$$R = \frac{\text{Covariance(X,Y)}}{SD(X)\ SD(Y)}$$

4. Results

A total number of 100 subjects have been studied. This includes 50 controls and 50 Type 2 Diabetic subjects. Controls: 50 (Males: 35& Females: 15), Type 2 Diabetic subjects: (50 (Males: 38&Females: 12). The concentrations of serum hs-CRP, ferritin and whole blood HbA_{1c} were analyzed and their values are shown in following tables.

Table 1: Shows Age and Sex Distribution of Controls and Type 2 Diabetic Subjects

No of subjects		Controls	Cases
		50	50
Age (years)	Mean ± SD	44.5 ± 7.8	45.6 ± 6.7
	Range	30 - 55	29 - 58
Gender	Males	35	38
	Females	15	12

A total of number of 100 subjects were included in the study. Among them, 50 were cases with type 2 diabetes mellitus and 50 were age and sex matched controls.Among the 50 controls studied, 35 were males and 15 were females with a mean age of 44.5 ± 7.8 years. Among the 50 type 2 diabetic subjects studied, 38 were males and 12 were females with mean age of 45.6 ± 6.7 years

Table 2: Shows Comparisons Of Body Mass Index (BMI), Waist Circumference (WC) and Waist-Hip Ratio (W/H Ratio) in Controls and Type 2 Diabetic Subjects

		Body Mass Index (kg/m^2)	Waist Circumference (cm)	Waist/Hip ratio
Controls	Mean ± SD	22.2 ± 3.62	85.06 ± 13.14	0.80 ± 0.16
	Range	16.04 - 29.6	58 - 118	0.56 - 1.56
Cases	Mean ± SD	25.55 ± 3.24	96.52 ± 10.28	0.98 ± 0.07
	Range	18.06 - 35.5	77 - 121	0.8 - 1.1
Cases v/s Controls	t-value*	3.33	11.06	0.18
	p-value	< 0.001	< 0.001	< 0.001
	Significance	HS	HS	HS

Shows comparisons of body mass index (BMI), waist circumference (WC) & waist/hip ratio (W/H Ratio) in contols and type 2 diabetic subjects.

It is seen from the table that the mean ± SDs of BMI, WC and W/H Ratio in controls are in the range of 22.2 ± 3.62 kg/m^2, 85.06 ± 13.14 cm & 0.80 ± 0.16, respectively.It is observed that the mean ± SDs of BMI, WC & W/H Ratio in type 2 diabetic subjects are in the range of 25.55 ± 3.24 kg/m^2, 96.52 ± 10.28 cm & 0.98 ± 0.07, respectively.It is evident that BMI, WC and W/H Ratio are increased in type 2 diabetic subjects as compared to healthy controls and the increase is statistically highly significant ($p < 0.001$)

Table 3: Shows Comparisons of Fasting Serum Glucose, High-Sensitivity C-Reactive Protein and Ferritn Levels in Controls and Type 2 Diabetic Subjects

		Fasting serum glucose (mg/dL)	hs-CRP (mg/dL)	Ferritin (mg/dL)
Controls	Mean ± SD	90.96 ± 9.61	1.79 ± 1.01	101.55 ± 78.76
	Range	68.4 - 112.6	0.4 - 4.02	19.6 - 389
Cases	Mean ± SD	150.17 ± 23.67	13.15 ± 15.74	263.34 ± 82.65
	Range	126.7 – 234	0.71 - 69.4	56 – 423
Cases v/s Controls	t-value*	59.16	11.37	161.79
	p-value	< 0.001	< 0.001	< 0.001
	Significance	HS	HS	HS

Shows comparisons of fasting serum glucose, high-sensitivity C-reactive protein (hs-CRP) and ferritin levels between contols and type 2 diabetic patients. It is seen from the table that mean ± SDs of fasting serum glucose, hs-CRP and ferritin levels in controls are in the range of 90.96 ± 9.61 mg/dL, 1.79 ± 1.01 mg/L and 101.55 ± 78.76 ng/mL, respectively. It is observed that mean ± SDs of fasting serum glucose, hs-CRP and ferritin levels in type 2 diabetic subjects are in the range of 150.17 ± 23.67 mg/dL, 13.15 ± 15.74 mg/L and 263.34 ± 82.65 ng/mL, respectively. It is evident that the fasting serum glucose, hs-CRP and ferritin levels are increased in type 2 diabetic subjects as compared to controls and the increase is statistically highly significant ($p < 0.001$).

Table 4: Shows Comparisons of Glycated Hemoglobin (HbA_{1C}), Levels in Controls and Type 2 Diabetic Subjects

		HbA_{1C} (%)
Controls	Mean ± SD	5.42 ± 0.47
	Range	4.2 - 7.6
Cases	Mean ± SD	8.59 ± 1.83
	Range	5.52 – 14
Cases v/s Controls	t-value*	3.17
	p-value	< 0.001
	Significance	HS

Shows comparisons of glycated hemoglobin (HbA_{1c}) levels between controls and type 2 diabetic subjects. It is seen from the table that mean ± SDs of HbA_{1c} levels in controls and type 2 diabetic subjects are 5.42 ± 0.47% & 8.59 ± 1.83% respectively. It is evident that the HbA_{1c} levels are increased in type 2 diabetic subjects as compared to controls and the increase is statistically highly significant ($p < 0.001$).

Table 5: Pearson's Correlation Coefficient in Type 2 Diabetic Subjects

Parameters	r-value	p-value	Significance
Fasting serum glucose and hs-CRP	0.33	0.001	S
Fasting serum glucose and Glycated hemoglobin	0.66	< 0.001	HS
hs-CRP and Glycated hemoglobin	0.433	0.001	S
Ferritin and Glycated hemoglobin	0.036	0.799	NS

Shows Pearson's correlation between fasting serum glucose, hs-CRP, ferritin, & HbA_{1c} in type 2 diabetic subjects. It is observed that there was a highly significant ($p < 0.001$) positive correlation existing between fasting serum glucose, fasting insulin, C-peptide, HOMA-IR & HbA_{1c}. There was significant ($p = 0.001$) correlation found between fasting serum glucose, hs-CRP & HbA_{1c}. There was no significant correlation found between ferritin & HbA_{1c}

Table 6: Validity of Glycated Hemoglobin Level For Glycemic Control With Cut-Off Level Of 6.9%

Sensitivity	90%
Specificity	94%
Positive predictive value	93.70%
Negative predictive value	90.30%
Accuracy	92%

It shows the diagnostic validity of glycated hemoglobin levels for glycemic control with cut-off level as 6.9%. It is evident that the glycated hemoglobin has the sensitivity of 90%, specificity of 94%, positive predictive value of 93.7%, negative predictive value of 90.3% and accuracy of 92% for predicting level of glycemic control.

5. Discussion

Diabetes mellitus is the commonest endocrine disorder. Systemic inflammatory activity plays a key role in the pathogenesis of vascular atherosclerosis, insulin resistance and type 2 diabetes mellitus. Inflammatory biomarkers may be of valuable tool for risk evaluation. Among them best evidence to date supports the use of high-sensitivity C-reactive protein to monitor cardiovascular risk in diabetic and nondiabetic individuals.[4]

In the present study we had evaluated 100 subjects including 50 controls and 50 type 2 diabetic subjects. Of the 50 type 2 diabetic subjects, 38 were males and 12 were females and among controls, 35 were males and 15 were females.

We studied high-sensitivity C-reactive protein, ferritin and glycated hemoglobin levels in controls and type 2 diabetic subjects.

The mean ± SDs of fasting serum glucose in controls and type 2 diabetic subjects were in the range of 90.96 ± 9.61 mg/dL and 150.17 ± 23.67 mg/dL, respectively. The mean value of fasting serum glucose was higher in type 2 diabetic subjects compared to controls. The increase is found to be statistically highly significant ($p < 0.001$) which is in accordance with Amanullah S et al[11], Mahajan A et al[12]& Meshram A et al.[13]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.[14]

The mean ± SDs of hs-CRP in controls and type 2 diabetic subjects were in the range of 1.79 ± 1.01 mg/L and 13.15 ± 15.74 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 ($p < 0.001$). This is in accordance with Ridkar M.P[15], Chamber J.C et al[16]&Coban E[17].It was also observed that hs-CRP levels positively correlated with fasting serum glucose and glycated hemoglobin which is in accordance with Wu T et al[18]and King D.E et al[19]

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.[4]

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.[5]

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.[20]

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.[21]

The mean ± SDs of ferritin in controls and type 2 diabetic subjects were in the range of 101.55 ± 78.76 ng/mL and 263.34 ± 82.65 ng/mL respectively. The mean value of ferritin in type 2 diabetic subjects was higher when compared to controls. The increase was found to be statistically highly significant ($p < 0.001$). This is in accordance with the Ford E.S[22]. In the present study we also found positive correlation existed between ferritin and HbA_{1c} in type 2 a diabetic subject which was statistically not significant. Ferritin is one of the key proteins regulating iron homeostasis, is widely available clinical biomarker to evaluate iron status. However, growing evidence has shown that even moderately increased iron stores represented by high-normal ferritin concentrations are associated with diabetes.[23]At least three possible explanations may account for elevated ferritin concentrations in patients with diabetes.

1) Elevated ferritin concentrations may represent elevated body iron stores.
2) Ferritin is also an acute-phase reactant and elevated ferritin concentrations may reflect inflammation.
3) Delayed clearance of glycosylated ferritin in patients with diabetes may have led to the elevated ferritin concentrations.[24]

Excess iron deposition in the liver may cause IR by interfering with the ability of insulin to suppress hepatic glucose production. Iron is autoxidized to form highly reactive, lipid soluble iron-oxygen complexes. These free radicals are powerful pro-oxidants which can change membrane properties and result in tissue damage. In addition iron accumulation in hepatocytes may interfere with insulin extracting capacity of the liver, & affect insulin synthesis and secretion in pancreas. Iron excess probably contributes initially to IR and subsequently to decreased insulin secretion.[25]

The mean ± SDs of HbA_{1c} in controls & type 2 diabetes were in the range of 5.42 ± 0.47 & 8.59 ± 1.83 % respectively. The mean value of HbA_{1c} was higher in type 2 diabetic subjects as compared to controls. The increase was statistically highly significant ($p < 0.001$). We also found positive correlation existed between HbA_{1c} and ferritin which was not statistically significant.Glycated hemoglobin concentration represents the integrated values of glucose over preceding 6 to 8 weeks since the rate of formation of HbA_{1c} is directly proportional to the concentration of glucose in blood.

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.[26]

Strength and further scope of the study:
This study demonstrates that the high levels of hs-CRP and ferritin as biomarkers for predicting cardiovascular complications in type 2 diabetes.The study also considers inclusion of interleukins (IL-1 & IL-6) as additional biomarkers in large number of subjects in future studies to decrease the variability's in data and to have a highly statistical significance.

6. Conclusion

Diabetes mellitus is an important health problem prevailing across the globe. Inflammation plays a significant role in the pathogenesis of diabetes and its associated complications. Evaluation of inflammatory biomarkers like high-sensitivity C-reactive protein and ferritin help in assessing cardiovascular risk. There is significant elevation in the levels of high-sensitivity C-reactive protein, ferritin, insulin, glycated hemoglobin, in type 2 diabetic subjects as compared to controls. There is strong association found between fasting serum glucose, high-sensitivity C-reactive protein and glycated hemoglobin. According to our results together with previous other studies findings, we suggest that the quantitative determination of high-sensitivity C-reactive protein and ferritin 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 and ferritin 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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