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Anju Varghese
Associate Professor,
Department of Biochemistry,
MOSC Medical College,
Kolenchery

Asha N S
Department of Biochemistry,
Govt. Medical College,
Trivandrum

Celine TM
Deparment of Community
Medicine, MOSC medical College,
Kolenchery

Prasanna D
Department of Biochemistry,
Govt. Medical College,
Trivandrum

Correspondence:
Dr. Anju Varghese,
Associate Professor,
Department of Biochemistry,
MOSC Medical College,
Kolenchery, Kerala, India.

Inflammatory markers in Type II Diabetes mellitus

Anju Varghese, Asha NS, Celine TM, Prasanna D

Abstract
The present study was carried out to investigate the levels of inflammatory markers and to observe the correlation of inflammatory markers with glycemic status in Type II diabetes. 35 diabetic patients, already diagnosed and attending diabetic clinic and 35 normal healthy subjects aged 30-70 years were recruited for the present study by convenient sampling technique. Mean values of TSA, C–reactive protein, Ceruloplasmin, FBS and HbA1c in diabetics was significantly higher when compared to normal subjects. No significant correlation has been found between inflammatory markers and glycemic status in type II diabetes mellitus. Significant positive correlation was observed between HbA1c and FBS. A chronic low grade inflammation was observed in diabetic patients. This is evident by significant increase in inflammatory markers. We recommend further detailed studies and tests to determine the possible risk of vascular complications in diabetic patients.

Keywords: Ceruloplasmin, C reactive protein, Glycated Haemoglobin, Inflammatory markers, Type II Diabetes mellitus.

Introduction
Inability to produce insulin or defect in its utilization results in diabetes mellitus. The incidence of diabetes is increasing in India with >62 million Indians currently diagnosed with diabetes mellitus [1]. International Diabetes Federation predicts as many as 438 million will have diabetes by 2030. Ninety percent of the present cases are type 2 diabetes [2]. Type 2 diabetes is strongly associated with obesity, currently a worldwide epidemic [3, 4]. Type II diabetes affects the immune system of the body. These immunological changes affect the cytokine release which alter the leukocytes and result in increased apoptosis. These changes suggest the involvement of inflammation in the pathogenesis of type II diabetes.
C–reactive protein (CRP) is the most commonly used inflammatory marker in the body. It is synthesised in liver in response to inflammatory cytokines such as interleukin-6 and tumor necrosis factor-α (TNF- α). Adipose tissue is a major source of endogenous TNF-α production; elevation in levels of TNF- α may be a critical mechanism by which fat cells induce peripheral insulin resistance [5].
Ceruloplasmin (Cp) is an acute-phase-responsive oxidase enzyme, primarily synthesised by the hepatic parenchymal cells, with small amounts apparently synthesised by macrophages and lymphocytes. Prior reports suggest that Cp is increased in diabetes mellitus, perhaps reflecting greater oxidant stress [6].
Sialic acid is a protein bound carbohydrate. Sialic acid is the group name for the acetylated neuraminic acids, such as N-acetyl neuraminic acid, N-glycolyl neuraminic acid and Di-acetyl neuraminic acid [7]. Only N-acetyl neuraminic acid has been isolated from human serum. It is seen attached to the non reducing ends of the carbohydrate chains of glycoproteins and glycolipids of various acute phase proteins. Elevated plasma sialic concentration is strongly related to the presence of microvascular complications in type 1 diabetes, especially retinopathy and nephropathy [8].
The present study was carried out to investigate the inflammatory markers levels and to observe the correlation of inflammatory markers with glycemic status in Type II diabetes.

Materials and Methods
The study was approved by Institutional Ethics Committee. A written, informed consent was obtained from all the participants. The study was performed in accordance with the "Ethical Guidelines for Biomedical Research on Human Participants, 2006" by the Indian Council of Medical Research and the Declaration of Helsinki, 2008.

Participants, Inclusion and exclusion criteria
35 diabetic patients, already diagnosed and attending diabetic clinic and 35 normal healthy subjects aged 30-70 years were recruited for the present study by convenient sampling technique. The following criteria were used to recruit the patients.

Inclusion criteria
1. Diabetic patients already diagnosed and attending diabetic clinic
2. Willing participants

Exclusion criteria
1. Pregnant women,
2. Age below 30 years
3. Diabetics with complications

Methods
Fasting serum sample was taken for analysis of plasma glucose[4], glycated haemoglobin (HbA1c) [9], serum CRP [10], serum Cp [11], serum TSA [12] by glucose oxidase-peroxidase method, cation exchange resin method, turbidimetric immunoassay method, copper oxidase method, thiobarbituric acid method respectively.

Data analysis
Data were analysed using Microsoft excel. Student 't' test was used to determine significance of difference between cases and controls. Pearson's correlation coefficient was used to determine the correlation between the variables. P value <0.05 is considered statistically significant.

Results
Results were presented in table no 1 to table no3. Mean values of TSA, CRP, Cp, FBS and HbA1c in diabetics was significantly higher when compared to normal subjects. Table 2 presents the correlation of inflammatory markers with glycemic profile-HbA1c and FBS. No significant correlation has been found between inflammatory markers and glycemic status in type II diabetes mellitus. Table 3 presents a significant positive correlation between HbA1c and FBS.

Table 1: Comparison of inflammatory markers and glycemic profile

Variable	Control	Case	P value
TSA	64.35±7.29	87.25±13.65	0.0001
Cp	27.84±6	43.72±9.69	0.0001
CRP	1.07±0.56	3.71±1.49	0.0001
HbA1c	5.14±0.69	7.83±1.70	0.0001
FBS	90.91±9.329	183.49±37.45	0.0001

Values are expressed in Mean ± SD.

Inflammatory marker	HbA1c	FBS
TSA	r=0.20	r=0.046
	P=0.258	P=0.792
Cp	r=0.037	r=0.138
	P=0.83	P=0.429
CRP	r=0.08	r=0.198
	P=0.65	P=0.255

Table 3: Correlation between HbA1c and FBS

Parameter	FBS
HbA1c	r=0.48
	P=0.004

Discussion
Low grade inflammation is usually associated with Type II diabetes mellitus. Markers of inflammation like CRP, Cp and TSA were found to be elevated in type II diabetes when compared to healthy controls. It was reported that TSA is a potent independent cardiovascular risk factor and is elevated in type 2 diabetes mellitus in some populations [13, 14]. Previous studies reported that elevated CRP concentrations increased with increasing HbA_{1c} levels in diabetic patients. These findings suggest an association between glycemic control and systemic inflammation in people with established diabetes [15]. It was reported that significant increase in FBS, PPBS and HbA1c levels in diabetics and diabetes with hypertension patients, the increase in HbA1c levels could be due to an increase in non enzymatic glycation of haemoglobin [16]. We agree with the earlier studies as we have observed significant increase in TSA, CRP, Cp, FBS and HbA1c levels in diabetic patients.
The increase in APP like CRP, Cp, TSA in diabetics illustrates that inflammatory status deteriorates in uncontrolled diabetes. Elevated glucose levels promote inflammation by increasing oxidative stress due to formation advanced glycation end products (AGE) and increased TNF [17]. Though there is significant correlation between HbA1c and FBS, no significant correlation is found between inflammatory markers and HbA1c.This is unlike the study by Yadav, *et al* [18] where there is significant correlation between inflammatory marker-ADA and HbA1c.

Limitations and future perspectives
The major limitation of the present study was less sample size. Also, we have not studied male and female comparison. In our future studies, we plan a multi-centre study with study with higher sample size to confirm the results and also to observe male and female differences.

Conclusion
A chronic low grade inflammation was observed in diabetic patients. This is evident by significant increase in inflammatory markers. We recommend further detailed studies and tests to determine the possible risk of vascular complications in diabetic patients.

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