**SERUM ISCHEMIA MODIFIED ALBUMIN LEVELS IN DIABETIC RETINOPATHY**

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**ABSTRACT**

**Objective:** To determine and compare the levels of ischemia modified albumin in controls and diabetic patients with and without retinopathy.

**Methods:** Diabetic Clinic of Lahore General Hospital was selected for the conduction of the study in collaboration with an ophthalmologist. Sixty subjects of either sex were chosen and were separated into 3 groups with 20 subjects in each group. Group 1 was of normal healthy controls, group 2 of diabetics without retinopathy and group 3 of diabetics with retinopathy. Diabetic retinopathy was diagnosed by an ophthalmologist by an indirect method using a 90D lens on slit lamp examination, and IMA (Ischemia Modified Albumin) levels were determined by rapid calorimetric method.

**Results:** The median (IQR) of serum levels of IMA in three groups were 0.51(0.43-0.54) in group I, 0.59(0.53-0.61) in group II and 0.63(0.59-0.71) Absorbance unit (ABSU) .A significantly higher IMA levels in diabetics with retinopathy were seen as compared to diabetic without retinopathy and control with a p values of 0.00.

**Conclusion:** Our study concludes that serum IMA levels raise as the diabetes progresses in its complications.

**Key words**: Serum Ischemia Modified Albumin (IMA), Diabetic Retinopathy

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**INTRODUCTION**

Diabetes mellitus is a group of metabolic diseases in which blood glucose levels are raised due to insufficient insulin secretion and insulin function.1 According to the International Diabetes Federation (IDF) in 2015 the prevalence of diabetes is almost 415 million around the world worldwide, and it is anticipated that by the year 2025, Pakistan will be having the fourth largest diabetic population in the world i.e. around 11.5 million people.2 Diabetic complications are classified broadly as acute and late complications which are further classified into microvascular complications. The three major types of diabetic microvascular complications are retinopathy, neuropathy and nephropathy.3 Diabetic Retinopathy is one of the adverse effects of diabetes mellitus and is the main cause of blindness amongst diabetics.4 It is a

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progressive and chronic disease of retina which is strongly related with the longer duration of hyperglycemia and comorbidities associated with diabetes mellitus such as hypertension.5

 Almost all type 1 diabetic patients and more than 60% of type 2 diabetic patients are estimated to have some type of retinopathy by first twenty years of the diabetes .6

 Human Serum Albumin (HSA), accounts for more than 60-65% of total plasma protein content. Ischemia-Modified Albumin (IMA) is the oxidatively modified form of human serum albumin which results due to the effect of oxidative stress products on HSA. Therefore IMA is considered as an oxidative stress marker in the human body.7 Metal ions like copper, nickel and cobalt bind to the N-terminal of HSA which is vulnerable to biochemical changes after it is exposed to ischemia and oxidative stress. These molecular modification leads to decreased capability of N terminal to combine metal ions.8 Raised levels of IMA have been seen in diabetic retinopathy. A study was done for estimating the levels of serum ischemia modified albumin in patients with diabetic retinopathy showed high sensitivity of IMA as in patients with diabetic retinopathy as compared to diabetic patients without retinopathy.9 Diabetic complications have a considerable influence on the quality of life of the patient. Therefore, it is essential to introduce effective screening and preventive strategies to detect the early signs of complications.

 The aim of the study was to determine the levels of serum ischemia modified albumin in diabetic retinopathy thus indicating underlying oxidative stress or ischemia.

**METHODS**

This cross sectional, comparative study was conducted in diabetic clinic of Lahore General Hospital Lahore from September 2014 to May 2015 after getting approval from research ethical committee of institute. After calculating the sample size, a total of sixty patients of either sex were included in this study and were divided in 3 groups having 20 subjects in each group. Group 1 was of normal healthy adults, group 2 was of diabetic diagnosed not to be suffering from retinopathy and group 3 was diabetic diagnosed with retinopathy. Smokers, pregnant women, hypertensive patients, patients with end stage renal disease, diabetic foot, autonomic neuropathy, liver cirrhosis, acute coronary syndrome, and cerebrovascular occlusion were excluded from the study on the basis of history and clinical examination. Presence of diabetic retinopathy was diagnosed by an ophthalmologist by an indirect method using a 90D lens on slit lamp examination.

 4ml of blood was collected for IMA and was routinely centrifuged within 1 hour for 15 minutes at 3000 revolutions per minute. Serum levels of IMA were estimated by a colorimetric assay which was explained by Bar-Or et al in which 200µl of serum was put in two separate test tubes followed by the addition of 2.50 μ L o f 0 .1% cobalt chloride (BDH prolab CoCl2 .6 H2O).To allow adequate binding of cobalt to albuminthe mixture was not disturbed for 10 mins after a mild mixing. Next 50 microliters of Dithiothretol (DTT) was added as an agent for colour development. Then 1.0 mL of 0.9% NaCl was added to both samples and the reaction was quenched for 2 mins. Absorbance was measured of both the test and control by using a spectrophotometer (microlab 3) at 470 nm, and reported in absorbance units (ABSU ).

 After cheking the normality of the data Kruskal –wallis test was applied for comparison of parameters between the three study groups and MannWhitney-U test was applied for the comparison between any two groups of the study . A p-value of < 0 .05 was taken as significant.

**RESULTS**

The mean SD of the age of group I subjects was 52.80±12.03 years, of group II subjects was 52.30±10.92 years and of group III subjects was 53.70±12.63 years. The body mass index of three groups was 21.92(19.75-22.87) kg/m2, 24.48(22.26-25.86) kg/m2 and 23.37(21.81-28.52) kg/m2 respectively.

 Comparison of IMA levels among the three study groups by Kruskal Wallis test revealed a significant difference of p=0.00 (Table 1). When comparison of IMA was done between the two groups of the study by Mann Whitney U test a significant difference of p=0.00 was seen (Table 2 ).

Table 1: Comparison of serum IMA levels in study groups by Kruskal Wallis test

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Parameter | Group I n=20 | Group II n=20 | Group III n=20 | Pvalue |
| IMA (ABSU) | 0.51 (0.43-0.54) | 0.59 (0.53-0.61) | 0.63 (0.59-0.71) | <0.00 |

Table 2: Comparison of serum IMA levels between groups by Mann Whitney U test

|  |  |  |
| --- | --- | --- |
| Parameter | Groups | P value |
| IMA (ABSU) | Group IGroup II | <0.001 |
| Group IGroup III | <0.001 |
| Group IIGroup III | <0.001 |

**DISCUSSION**

The outcome of this study shows that IMA is raised in diabetic with retinopathy as compared to diabetics without retinopathy and control. Comparable results revealed by Turk et al., and Reddy et al., have proved that IMA is a sensitive as well as specific biochemical marker for the evaluation of diabetic retinopathy.10,11 In contradiction to our results Chawla et al., have reported a nonsignificant difference in serum levels of IMA on comparing them among diabetics with and without vascular complications. However in their study only 4 out of 66 diabetics with microvascular angiopathies had retinopathy.

 Higher levels of IMA have been seen in diabetic patients .12 The higher levels are thought to be because of uninhibited hyperglycemia induced oxidative stress, that occurs on the endothelial cell and consequently released reactive oxygen species (ROS) modifies the albumin .13 These ROS impair the N-terminal portion of human albumin by causing the separation of two terminal amino acids and also promotes the oxidation of cys 34 of HSA which results in decreased binding of cobalt to albumin resulting in production of ischemia modified albumin.7 An in vitro investigation in 2006 by Roy et al., showed a positive association between the development of ischemia modified albumin and generation of ROS. They also documented that specifically OH leads to formation of IMA, by decreasing albumin’s Co2+ binding capacity.14

 Abundant oxidative stress on endothelium of the blood vessels due to hyperglycemia causes widespread endothelial damage leading to ischemia and formation of circulating IMA.15

 The formation of reactive oxygen species leads to endothelial damage and ischemia which causes the production of IMA. So, Ischemia modified albumin can act as a valuable and an economical biomarker for detection of diabetic retinopathy in diabetic patients so as to prevent blindness.

**CONCLUSION**

Serum levels of IMA are raised in diabetics with retinopathy as compared to diabetics without retinopathy. Therefore, it can be concluded that serum ischemia modified albumin levels can act as a prompt biomarker for the detection and progression of diabetic retinopathy in diabetic patients.

**ETHICAL APPROVAL**

The study was approved from Ethical Review Committee of Postgraduate Medical Institute, Lahore, Pakistan.

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**Authors’ Contribution:**

**src:** Principal author editing

**zrc:** Write up

**ki:** Proof Reading, data collection

**MS:** Concept and design of the work, proof reading

**erc:** Proof Reading, data collection

**hnl:** Literature research

**sy:** Data analysis