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RESEARCH ARTICLE

ADIPOCYTE FATTY ACID BINDING PROTEIN (A-FABP) AS A NOVEL BIOCHEMICAL MARKER OF DIABETIC RETINOPATHY

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Abstract

Introduction: Diabetes mellitus is acomplex metabolic disorder associated with increased risk of microvascular and macrovascular disease characterized by chronic hyperglycaemia resulting from defect in insulin secretion, insulin action, or both. Diabetic retinopathy (DR) causes visual impairment as a result of long term accumulated damaged to the small blood vessels in the retina.Adipocyte fatty acid binding protein(AFABP), been suggested as a third adipokine, in addition to leptin and adiponectin. AFABP might have a role in the proliferation of endothelial cells, as well as in angiogenesis. A-FABP levels were determined in subjects witout diabetes mellitus, with type 2 diabetes mellitus without DR and with DR at admission in order to investigate a possible association of A-FABP to the increased risk of incidence of DR.

Material and methods: This study was done on non-diabetic (*n=25*) and Type 2 diabetes subjectswith*(n=25)* and without retinopathy *(n=25)* who visited HAHC hospital. Blood glucose (fasting and post prandial), glycated hemoglobin(HbA1c), urea, creatinine, uric acid, total protein, serum albumin,serum electrolytes (sodium, potassiumand chloride), totalcholesterol,triglyceride, high density lipoprotein(HDL), low density lipoprotein (LDL), very low density lipoprotein (VLDL) and and AFABP were measured .

Result: The mean values of blood glucose (fasting and post prandial),HbA1C,urea, creatinine , TG, LDL VLDL and AFABP were higher in diabetic subjectswith diabetic retinopathy in comparison to diabetic subjects without retinopathy and subjects without diabetes mellitus and were highly significant statistically.($p<0.01$). The mean value of HDL was lower in diabetic subjects with diabetic retinopathy in comparison to diabetic subjects without retinopathy and subjects without diabetes mellitus and was highly significant statistically.

Conclusion: The study helps in associating AFABP as an early biochemical marker for identifying onset of diabetic retinopathy in subjects with diabetes mellitus at an early stage.

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Introduction:-

The frequency of diabetes is increasing due to the growing population, aging urbanization, obesity, and decrease in physical activity [1]. International Diabetes Federation (IDF,2019) states that approximately 463 million adults (20-79 years) were living with diabetes; by 2045 this will rise to 700 million [2].Type 2 diabetes mellitus is associated with a high rate of complications related to cardiovascular disease and diabetic nephropathy, retinopathy, and neuropathy. The most common microvascular complication of diabetes mellitus is diabetic retinopathy [3].The prevalence of diabetic retinopathy is strongly related to the duration of diabetes. It is the most frequent cause of new cases of blindness among adults aged 20 to 74 years [4].

DR causes visual impairment as a result of long-term accumulated damage to the small blood vessels in the retina [5]. Diabetic retinopathy progresses from mild non-proliferative abnormalities, (characterized by increased vascular permeability) to moderate and severe non-proliferative diabetic retinopathy (NPDR), characterized by vascular closure) to proliferative diabetic retinopathy (PDR), characterized by the growth of new blood vessels on the retina and posterior surface of the vitreous. In the younger-onset group, 86% of blindness is attributable to diabetic retinopathy. In the older-onset group, in which other eye diseases were common, one-third of the cases of blindness are due to diabetic retinopathy. Up to 21% of patients with type 2 diabetes have retinopathy at the time of the first diagnosis of diabetes, and most develop some degree of retinopathy over time [6]. It has been reported that a breach in the blood-retinal barrier triggers an increase in vascular permeability, which in turn causes macular edema [7,8].

Adipocyte fatty acid-binding protein (AFABP), first detected in adipose tissue and mature adipocytes has been suggested as a third adipokine, in addition to leptin and adiponectin [9]. A-FABP belongs to a family of fatty acid-binding proteins, which are small cytoplasmic proteins expressed in a highly tissue-specific manner, it is thought to be important in mediating intracellular fatty acid trafficking and energy metabolis. Expression of A-FABP is highly induced during adipocyte differentiation and transcriptionally controlled by peroxisome proliferator-activated receptor (PPAR) γ agonists, fatty acids, dexamethasone, and insulin [10].

In the mature retina, following the complete regression of the hyaloid vessels, faint and ubiquitous A-FABP immunoreactivity is detected throughout the retinal layers. Since A-FABP induction reaches its maximum levels at the time of completion and maturation of the inner retinal vasculature, A- FABP could play a role during normal retinal vascularization [11]. A-FABP has been implicated in the pathology of diabetes and macrovascular diseases. Thereforthe chief aim of our study was to determine A-FABP levels in type 2 diabetic patients with and without DR at admission to investigate a possible contribution of A- FABP to the increased risk of diabetic retinopathy (DR). Additionally, we evaluated the change in blood glucose levels, HbA1c, kidney function test, and lipid profile as biochemical parameters along with a subsequent comparison with healthy non-diabetic subjects.

Material and Method:-

The case-control study was done on Type 2 diabetics and diabetic retinopathy patients who visited the Department of Opthalmology at HIMSR,HAHC hospital, New Delhi after obtaining due consent. The study included 25 type 2 diabetic without retinopathy patients and 25 diabetic retinopathy patients, and 25 non-diabetic healthy subjects. The subjects were aged 30-60 years. Subjects with blindness/ compromised vision due to deficiency of Vitamin A, glaucoma, corneal disease, and other posterior segment diseases were excluded.

The anthropometric study was done and biochemical parameters on the fasting blood sample of subjects were analyzed for blood glucose fasting, post parandial, HbA1c, urea,creatinine, uric acid, total protein, albumin, total cholesterol, triglycerides, high-density lipoprotein were analyzed by a fully automated analyzer. The adipocyte fatty acid-binding protein (AFABP) was analyzed by ELISA technique by kit from Krishgen limited.

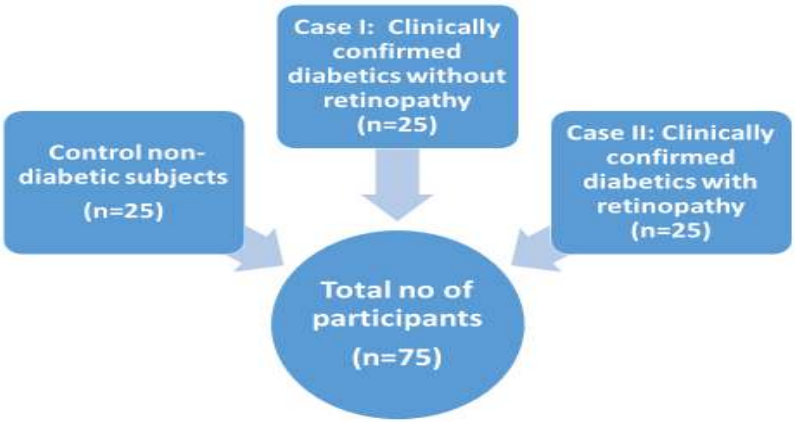

Fig 1:- Study design and selection of subjects.

Results:-

Anthropometric Data

Anthropometric data (Figure :2) depicts that the difference in mean value of BMI of healthy non diabetic control (group 1)versus that of cases of Type II diabetic mellitus without retinopathy (group 2) was significant (group 1 [23.24 ± 1.2] vs group 2 [24.56 ± 2.3] . p-value 0.14). Highly significant value for BMI was observed in BMI of healthy non diabetic control versus that of cases of type IIdiabetic mellitus with retinopathy (group 3) (group 1 [23.24 ± 1.2] vs group 3 [25.43± 2.5], p-value being 0.0003). Waist hip ratio was highly significant in group 1 vs group 2 (group 1 [0.94±0.01] vs group 2[0.96±0.01], p-value being 0.0001) , group 1 vs group 3 (group 1 [0.94 ±0.01] vs group 3 [0.97±0.01], p-value being 0.0001) and group 2 vs group 3 (group 1 [0.96±0.01] vs group 3 [0.97±0.01] . Mean value of systolic blood pressure was significant in group 1 versus group 2 and group 1 versus group 3 (group 1 [118.72 ±7.5] vs group 2[123.59±9.1], p-value 0.04) (group 1 [118.72±7.5] vs group 3[122.76±5.5], p-value 0.034).

Blood Sugar Profile

Blood sugar profile (Figure : 3) depicts that the difference in the mean value of fasting blood sugar of healthy was highly significant in all the groups. The difference in the mean value of fasting blood sugar in non-diabetic control (group 1) versus that of the case of type II diabetes mellitus without retinopathy (group 2) was highly significant (group 1 [93.64± 5.6] versus group 2 [171.7 ± 6.5], p-value 0.0001). Highly significant values were also seen in group 1 vs group 3 (group 1 [93.64±5.6] vs group 3 [207.87± 6.3], p-value 0.0001) and group 2 versus group 3 (group 2 [171.77 ±6.5] vs group 3 [207.87±6.3] , p-value 0.0010) . The difference in mean value of postprandial blood sugar was highly significant in all groups, group 1 versus group 2 (group 1 [118.8± 10.4] vs group 2 [252.03 ± 9.2] , p-value 0.0001) , group 1 versus group 3(group 1[118.8 ±10.4] vs group 3 [261.41 ± 10.1] , p-value 0.0001) and group 2 versus group 3 (group 2[252.03 ±9.2] vs group 3 [261.41 ± 10.1] , p-value 0.0012). The difference in mean value of HbA1C was highly significant in two groups, group 1 versus group 2(group 1 [5.28 ± 0.3] vs group 2 [10.14±0.8], p-value 0.0001) and group 1 versus group 3 (group 1[5.28± 0.3] vs group 3 [9.98 ±0.8], p-value 0.0001).

Kidney Function Profile

Kidney function profile (Figure : 4) depicts that the difference in mean value of urea was highly significant in non diabetic control (group 1) versus that in cases of type II diabetes mellitus with retinopathy (group 3) (group 1 [27.86 ± 2.4] vs group 3 [33.63 ±2.7], p-value 0.0001) and also in cases with type II diabetes mellitus without retinopathy (group 2) versus that with diabetic retinopathy)group 3) (group 2 [27.78 ±2.2] vs group 3 [33.63±2.7], p-value 0.0001). The difference in mean value of serum creatinine was highly significant in group 1 versus group 3 (group 1[0.68±0.1] vs group 3 [0.97±0.3], p-value 0.001) and group 2 versus group 3(group 2 [0.72± 0.2] vs group 3 [0.97±0.3] , p-value 0.0003). The difference in mean value of total protein was highly significant in group 1 versus group 2 (group 1 [7.38±0.6] vs group 2 [6.74±0.7], p-value 0.001) and also in group 1 versus group 3 (group 1[7.34 ±0.6] vs group 3 [6.62±1] , p-value 0.001). The difference in mean value of serum albumin was significant only in group 1 versus group 3 (group 1[3.98±0.4] vs group 3 [3.51± 0.8], p-value 0.011). The difference in mean value of sodium was significant in group 1 versus group 2(group 1[139 ± 3.5] vs group 2 [136.45± 5.3] , p-value 0.50) and highly significant in group 1 versus group 3(group 1 [139± 3.5] vs group 3 [132

± 5.15] , p-value 0.0001) and group 2 versus group 3 (group 2 [136.4 ±5.3] vs group 3 [132 ±5 .15] , p-value 0.004).The difference in mean value of serum chloride was significant in group 1 versus group 3(group 1 [102.2 ± 5.1] vs group 3[106 ± 6.4] , p-value 0.021) and in group 2 versus group 3 (group 2 [101.48 ± 4.4] vs group 3 [106 ± 6.4] , p-value 0.005)

Lipid Profile

Lipid profile(Figure no 5) depicts that the difference in mean value of serum triglyceride was highly significant in all groups, group 1 versus group 2 (group 1[117.88 ± 7.5] vs group 2 [133.34± 5.85] , p-value 0.0001) , group 1 versus group 3 (group 1[117.88± 7.5] versus group 3 [143.82 ± 3.21] , p-value 0.0001) and in group 2 versus group 3 (group 2 [133.34 ±5.85] vs group 3 [143.32 ±3.2], p-value 0.0001). The difference in mean value of HDL was highly significant in two groups, group 1 versus group 2(group 1[46.22 ±3.57] vs group 2 [37.54 ±3.37] , p-value 0.0001) and in group 1 versus group 3 (group 1[46.22 ± 3.57] vs group 3 [36.99 ± 2.24] , p-value 0.0001). The difference in mean value of serum LDL was highly significant in all groups, group 1 versus group 2 (group 1[78.0 ±6.56] vs group 2 [84.5 ±7.43], p-value 0.0022) , group 1 versus group 3(group 1 [78.0 ±6.56] vs group 3 [94.95 ±7.4] , p-value 0.0001) and group 2 versus group 3 (group 2 [84.5 ±7.43] vs group 3 [94.95 ±7.4] , p-value 0.0001). The difference in mean value of serum VLDL was highly significant in all groups, group 1 versus group 2 (group 1 [23.82 ± 1.81] vs group 2 [26.23 ± 1.1] , p-value 0.0001) , group 1 versus group 3 (group 1 [23.82 ± 1.81] vs group 3 [33.16 ± 1.62] , p-value 0.0001) and group 2 versus group 3 (group 2 [26.23 ±1.1] vs group 3 [33.16± 1.62] , p-value 0.0001).

Adipocyte fatty acid binding protein (A-FABP)

Adipocyte fatty acid binding protein (Figure no 6) depicts that the difference in mean value of serum AFABP was highly significant in all groups , group 1 versus 2 (group 1 [4.42 ±0.72] vs group 3[5.78± 0.07], p-value 0.0001) , group 1 versus group 3 (group 1 [4.42± 0.72] vs group 3 [7.9 ±0.02] , p-value 0.0001) and group 2 versus group 3 (group 2 [5.78± 0.07] vs group 3[7.9 ± 0.02] , p-value 0.0001)

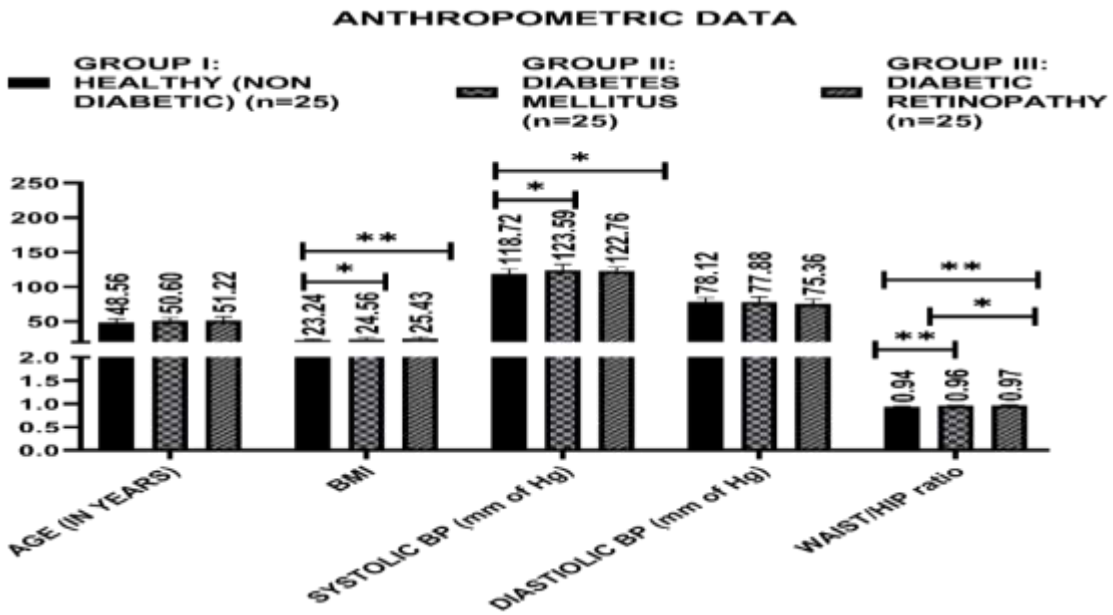

Fig 2:- Evaluation of Anthropometric data: Values are expressed in mean ±SEM, *p<0.05 significant,** p<0.01. BMI: Body-mass index.

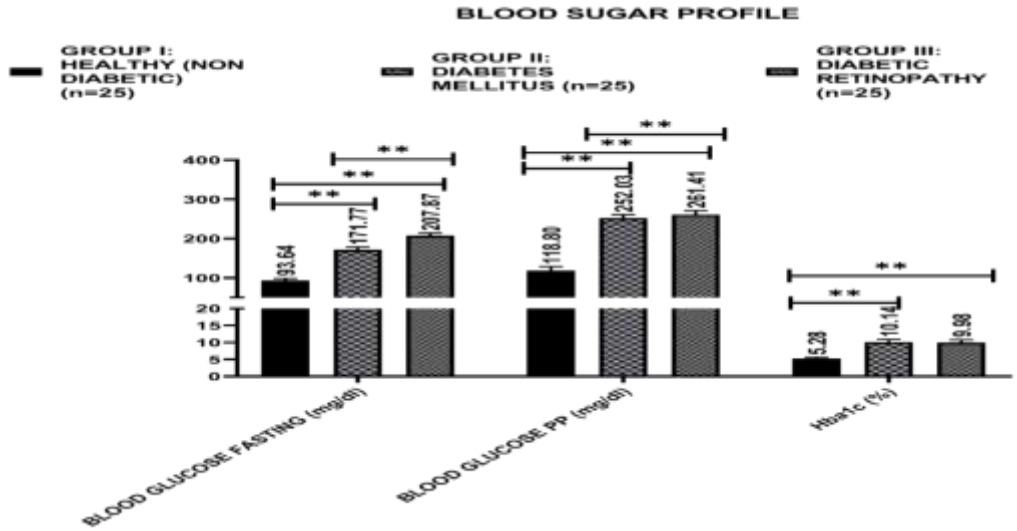

Fig 3:- Evaluation of blood sugar profile. Values are expressed in mean ±SEM, *p<0.05 significant, ** p<0.01. HbA1c: Glycated hemoglobin.

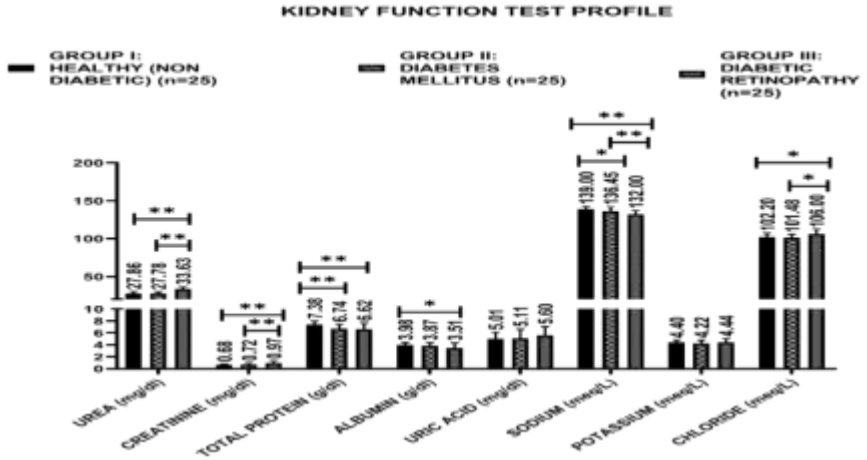

Fig 4:- Evaluation of the kidney function test. Values are expressed in mean ±SEM. ns: non-significant, *p<0.05 significant, ** p<0.01.

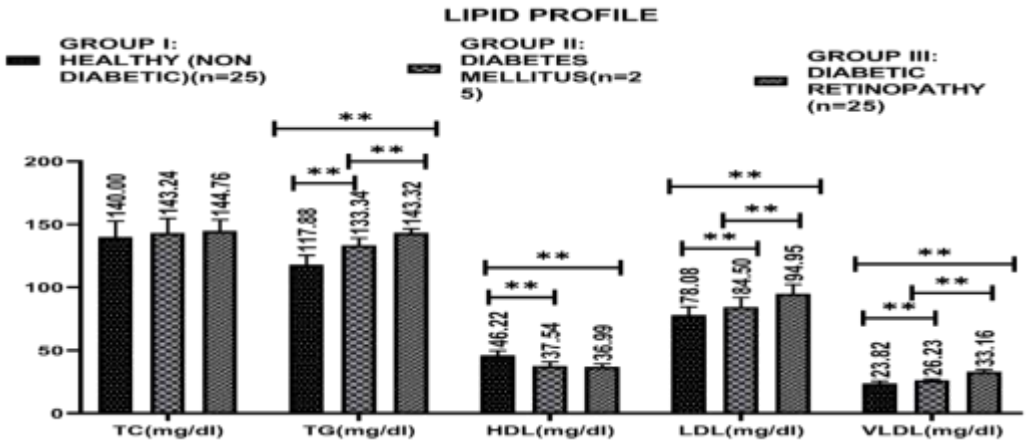

Fig 5:- Evaluation lipid profile test. Values are expressed in mean ±SEM. ns: non-significant, *p<0.05 significant,** p<0.01.

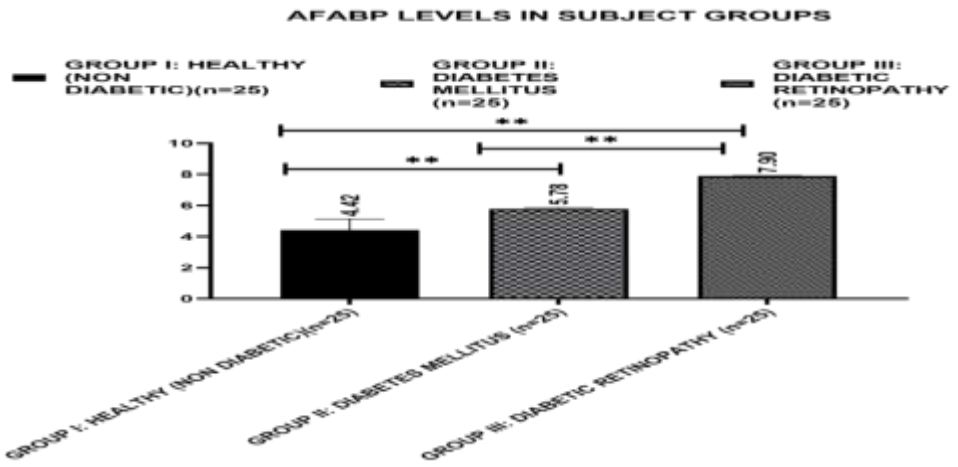

Fig 6:- Evaluation A-FABP levels. Values are expressed in mean ±SEM. ns: non-significant, *p<0.05 significant,** p<0.01.

Discussion:-

Diabetes is the most frequent endocrine disease in developed countries and one of the most common non-communicable diseases (NCDs) globally, estimated to have affected more than 371 million people in 2012 and projected to affect 552 million by 2030 [12]. DR is one of the most common microvascular complications of diabetes mellitus (DM) and a leading cause of visual impairment and preventable blindness in working-age adults in developed countries is has been estimated to represent 12% of blindness in developed countries [13].

In our study, a highly significant difference in the mean value of BMI was observed between healthy non-diabetic subjects and type 2 diabetes mellitus subjects with retinopathy. Increased body mass index has been linked to an increased risk of diabetic retinopathy. Our study is in line with other studies [14-16] which shows a direct relationship of BMI in subjects with diabetes mellitus with the risk of developing diabetic retinopathy.

In our study, the difference in the mean value of waist to hip ratio was highly significant in all groups and was in line with the findings of other studies which suggest that increase in waist to hip ratio is associated with significantly higher rates of diabetic retinopathy [17,18].The difference in the mean value of systolic blood pressure was significant in non-diabetic subjects versus diabetes mellitus subjects without retinopathy versus diabetes mellitus subjects with retinopathy was significant which is in line with other studies which showed an association between hypertension and the presence and severity of retinopathy in people with diabetes. Increased blood pressure has been hypothesized, through the effects of increased blood flow, to damage the retinal capillary endothelial cells in eyes of people with diabetes [19].

The difference in the mean value of fasting and postprandial blood sugar was highly significant in non-diabetic subjects versus diabetes mellitus subjects without retinopathy versus diabetes mellitus subjects with retinopathy which is in line with other studies that have consistently shown that uncontrolled blood glucose level is a major risk factor in the pathogenesis of macrovascular and microvascular disease in subjects with DM leading to diabetic retinopathy [20]. The difference in the mean value of glycated Hb was significant in non-diabetic subjects versus diabetes mellitus subjects without retinopathy versus diabetes mellitus subjects with retinopathy was highly significant which is in line with the observation of study by Yun et al. in which it was concluded that DR was significantly more in patients having higher levels of HbA1c [21]. HbA1c is a good indicator of glycemic control as it can help diabetic individuals in the deterrence of microvascular complications especially DR. Complications of DR with respect to HbA1c values have been studied by many authors, and almost all the studies were in accord and pointed out that elevated HbA1c level resulted in worsening of DR [22].

The difference in mean value of urea and creatinine was highly significant in non-diabetic subjects versus diabetic patients with retinopathy and diabetes mellitus subjects without retinopathy versus diabetes mellitus subjects with retinopathy. The difference in the mean value of protein was highly significant in non-diabetic subjects versus diabetic patients without retinopathy and diabetic patients with retinopathy. The difference in the mean value of

serum albumin was only significant in non-diabetic subjects versus diabetic patients with retinopathy. The mean value of serum sodium was significant in non-diabetic subjects versus diabetic patients without retinopathy and highly significant in non-diabetic subjects versus diabetic patients with retinopathy and diabetes mellitus subjects without retinopathy versus diabetes mellitus subjects with retinopathy. The mean value of chloride was significant in non-diabetic subjects versus diabetic patients with retinopathy and diabetes mellitus subjects without retinopathy versus diabetes mellitus subjects with retinopathy.

Epidemiological studies have shown that diabetic retinopathy and nephropathy are closely associated [23] Both diabetic retinopathy (DR) and nephropathy are typical microvascular complications of diabetes mellitus (DM). It is well known that the prevalence of chronic kidney disease (CKD) and DR increase proportionally to the disease duration in type 2 diabetes. The common pathological abnormalities within the retinal and glomerular microvascular beds are the progressive narrowing and eventual occlusion of vascular lumina within the retina and glomerulus [24,25]. The increase in the level of serum urea and creatinine in our study in subjects with diabetic retinopathy was also supported by a similar finding in another study[26]. The finding of this study is in line with a study which had shown that diabetic patient had a lower level of serum total protein either due to increased excretion due to nephropathy or due to a decrease in production due to defect in insulin secretion or action or both [27].

Hyperglycemia is one of the major causes of progressive renal damage. An increase in urea level is seen when there is damage to the kidney in the presence of high blood sugar levels in diabetic patients [18]. The statistically significant difference in serum albumin is in line with the study that had shown that serum albumin was significantly associated with the severity of retinopathy and neuropathy [28].Agoro et al showed that total protein in type 2 diabetes mellitus was decreased significantly statistically due to hypervolemia as a result of the increased osmolality of the blood caused by hyperglycemia [29].The decrease in the level of serum sodium and chloride levels in our study is in line with another study which had shown a significant reduction in serum sodium and chloride levels with an increase in fasting blood glucose levels [30].

The cause of dysnatremia in diabetes is osmotic diuresis. In patients with uncontrolled diabetes serum, sodium levels may vary depending upon the balance between the hyperglycemia-induced water movement out of the cells that lower sodium and the glucosuria-induced osmotic diuresis, which increases sodium.Elevations in blood glucose levels draw water out of the cells into extracellular place leading to hyponatremia [31,32].

The difference in the mean value of triglyceride, LDL, and VLDL was highly significant in all study groups. The difference in the mean value of HDL, LDL and triglycerides were highly significant in non-diabetic subjects versus diabetes mellitus subjects without retinopathy versus diabetes mellitus subjects with retinopathy. The findings of our study is in line with the study by Y C Chang et al [33] which demonstrated that diabetics with raised LDL levels showed a higher prevalence of Diabetic retinopathy and study by Cetin EN et al [34]which had concluded that triglyceride level was related to all levels of retinopathy. The difference in the mean value of cholesterol was insignificant in all the study groups which is in contrast to the studies by Al-Bdour et al [35]and Larsson et al [36]which had found significant correlation of cholesterol with the onset of DR. High lipid levels are known to cause endothelial dysfunction due to reduced bioavailability of nitric oxide and this endothelial dysfunction was suggested to play a role in retinal exudate formation in DR (37).

They may not cause direct injury to the endothelium but are rather involved in the pathogenesis of DME only **via** exudation of lipids through damaged retinal vasculature. It was also reported that the peroxidation of lipids in lipoproteins in the vascular wall leads to local production of reactive carbonyl species that mediate recruitment of macrophages, cellular activation and proliferation, and also chemical modification of vascular proteins by advanced lipoxidation end-products which affect both the structure and function of the vascular wall [38].

Consequently, it was proposed that hyperlipidemia might contribute to DR and macular edema by endothelial dysfunction and breakdown of the blood-retinal barrier leading to exudation of serum lipids and lipoproteins[39]. The difference in the mean value of adipocyte fatty acid-binding protein (AFABP)was highly significant in all study groups. The difference in the mean value of AFABP was highly significant in non-diabetic subjects versus diabetes mellitus subjects without retinopathy versus diabetes mellitus subjects with retinopathy.A considerable number of studies have shown that plasma concentrations of FABP4 is increased in obesity and T2DM, and that circulating FABP4 levels are correlated with certain clinical parameters, such as body mass index, insulin resistance, and

dyslipidemia [40]. Previous studies have also shown a correlation between various parameter of lipid profile and fatty acid binding protein [41].

Our finding is in line with another study which has concluded AFABP to be a novel biomarker for prediction of diabetic retinopathy in type 2 diabetes mellitus patient [42].Adipocyte fatty acid-binding protein (A-FABP, also known as aP2 or FABP4) is highly expressed in mature adipocytes, accounting for approximately 6% of their total soluble protein [43].Adipocyte fatty acid-binding protein (A-FABP) is a lipid chaperone protein mainly expressed in adipocytes and macrophages. It is also secreted by adipocytes and circulates in the bloodstream [44].

FABPs, a family of intracellular lipid chaperones, are engaged in the transport of fatty acids to specific organelles in the cell, including mitochondria, peroxisomes, the nucleus, and the endoplasmic reticulum. The human FABP4 consists of 132 amino acids. Its molecular mass has been assessed at 14.6 kDa. FABP4 expression markedly increases at the time of adipocyte differentiation [40,45]. Circulating FABP4 induces insulin resistance, which is an independent biomarker of proliferative retinopathy [46].

Lipopolysaccharides (LPS) stimulate FABP4 transcription through JNK, which in turn induces c-Jun recruitment to a highly conserved activator protein-1 recognition site within the proximal region of the FABP4 promoter[40]. LPS-binding protein is involved in the immune response triggered by inflammatory injury characteristic of DR. Moreover, FABP4 is an obligatory mediator coupling toxic lipids (i.e., saturated fatty acids) to endoplasmic reticulum stress in macrophages in vitro and in vivo[47]. Endoplasmic reticulum stress represents an initial event in retina pathogenesis in diabetes[42,48].

The possible metabolic derrangements leading to diabetic retinopathy found in our study has been summarized in figure 7. A significant association of AFABP as an early biochemical marker of diabetic retinopathy in patients with type 2 diabetes isa finding of the present study.

Conclusion:-

A significant and novel finding of this study is the use of adipocyte fatty acid binding protein as an early biochemical marker of diabetic retinopathy in patients with type 2 diabetes. The present findings support the conclusion that A- FABP contributes to the increased risk of retinopathy in subjects suffering from uncontrolled type 2 diabetes mellitus. In the future, determining the varied properties of A-FABP and detecting their levels in multicentric studies and meta-analysis encompassing different phenotypes can also serve as a good alternative approach.The study would have been moe conclusive if the sample size was more and the duration of study was longer. A small sample, ethnic background and incomplete coverage of followups limits the scope of our results. Therefore, validation on a large population and different genetic backgrounds can reflect the true implications.

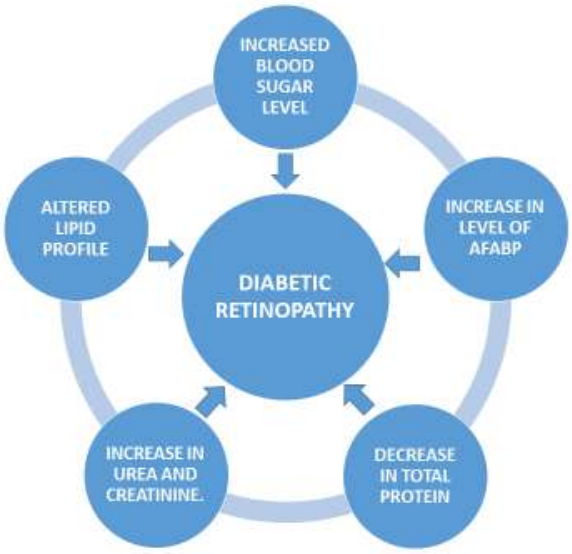

Fig 7:- Metabolic derrangements leading to Diabetic retinopathy.

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Conflict of Interest
On behalf of all authors the corresponding author states that there is no conflict of interest.

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Authors' contributions:
Shweta Singh has conceptualized the study. Bhumika Upadhyay and HinaYaseen have designed the study and reviewed the literature along with analysis of data. Shweta Singh, Bhumika Upadhyay, Hina Yaseen and HinaKausar have prepared manuscript draft. Dr Chandra Mohan Kumar has critically reviewed the manuscript. All authors have contributed towards drafting, revision and editing of the final version of the article

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