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Serum Levels of Inflammatory Marker Chemerin and Apelin in Type2 Diabetes Mellitus Patients with Diabetic Retinopathy in A Tertiary Care Centre, Tamil Nadu: A Case –Control Study

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ABSTRACT

Background:Diabetes Mellitus is a metabolic disease with significant health impacts, including cardiovascular disease and retinopathy, exacerbated by uncontrolled glucose levels. The onset of Diabetic Retinopathy (DR) is closely associated with oxidative damage, inflammation, and several proangiogenic cytokines. Chemerin and apelin are pleiotropic peptide cytokine and it is involved in adipogenesis, glucose metabolism and inflammation.

Objective: To assess the levels of inflammatory marker chemerin and apelin in T2DM patients with and without diabetic retinopathy.

Materials and Methods:This study was conducted at St.Peters Medical College Hospital & Research Institute,Hosur,Tamilnadu. Duration of study period was 1year. Totally 110 healthy control, and 110 patients without DR and 110 patients with DR were included. Serum samples were tested for chemerin and apelin by ELISA method. Biochemical parameters and ophthalmological examination findings of the participants were recorded.

Results and Discussion:In this study,we recruited 330 participants, including110 healthy individuals in group 1, 110 patients T2DM without DR in group2 and 110 T2DM with DR in group 3. Out of 110 DR ,77 were males (70%) and 33 (30%) females. Serum chemerin andapelin level was significantly higher in group 1 than in group2 and group 3.

Conclusion: patients with T2DM with DR showed higher Serum chemerin and apelin levels than those with T2DM without DR and healthy individuals. High levels of chemerin and apelin paved the pathogenesis diabetic retinopathy by enhancing inflammation, insulin resistance and angiogenesis factor. Early diagnosis of T2DM provides better treatment and reduce risk of diabetic retinopathy.

Keywords: *Chemerin, Apelin, Diabetes Mellitus, Diabetic Retinopathy*

1. INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) stems from a chronic metabolic disorder of enduring concern. The condition relates to insulin carving out bubbles in insulin secretion as well as resistance, leading to an increase in blood glucose levels. Due to its growing prevalence, T2DM along with the complications that are associated with it, has become a global health issue and

burden. One main complication of T2DM is Diabetic Retinopathy (DR). DR is a widely spread microvascular complication of T2DM that often leads to loss of vision if left untreated [1].

T2DM and diabetic retinopathy (DR) are strongly correlated, especially with new studies surfacing. [2] highlighted the fact that individuals with T2DM have a disproportionately higher chance of developing DR compared with those without diabetes which calls for early intervention and frequent screening. The International Diabetes Federation (IDF) conjectured that in 2019, diabetes mellitus (DM) was estimated to have 463 million cases, with the numbers anticipated to soar to 700 million by 2045. Diabetic DR continues to be a prevalent factor in vision threatening complications of DM while being the most significant preventable cause of blindness among adults in the workforce [3].

In people suffering from diabetes globally, diabetic retinopathy has become a leading cause of vision-threatening disability and blindness. It's this high level of impact in emphasizing the widespread prevalence along with the associated risk factors of DR that [4] have not only observed but also shed light on.[5] Remark that macular edema is a common complication of DR due to fluid build-up in the macula, it greatly impairs visual acuity. The more advanced stages of DR may progress to proliferative diabetic retinopathy (PDR) which can cause serious complications such as vitreous hemorrhage further severely impacting vision impairment [6]. As well, people with DR have an added probability of being diagnosed with glaucoma and cataracts [7]. The psychosocial impacts of DR are also severe and adversely affects the patient's overall quality of life by vision-specific functioning and psychological health [8].

In combination, these studies stress the diverse effects of DR which require prompt attention for efficient control and treatment methods to minimize the impact on visual health and wellbeing. Management of diabetes with DR requires immediate attention.Originally termed as TIG2 in the late 1990s as a result of studying the impact of retinoids on skin cell, Chemerin was later discovered in 2003 to be a ligand for G-protein coupled receptor CMKLR1[9].

The discovery associated chemerin with the chemokine family and elucidated its function in guiding the migration of immune cells to inflamed tissues. Chemerin is synthesized as a precursor protein, prochemerin, which becomes active by cleavage and binds to CMKLR1, modulating immune reactions and catalytic activities like adipocyte maturation, glucose metabolism, and insulin action[10].These realties underscore the in doubtful impacts of chemerin on obesity and type 2 diabetes mellitus (T2DM). Chemerin also binds to the receptors GPR1 and CCRL2 where it also has roles in other processes like energy balance in several tissues. Increased concentrations of chemerin have been linked to deranged metabolism, inflammatory conditions, cardiovascular pathologies, and hence could serve as a useful biomarker and a target for treatment [11].

Apelin is a peptide classed as an adipokine which is synthesized in the brain, heart, skeletal muscles, and stomach where it exerts its effects by attaching to the G-protein coupled receptor APJ which is a receptor of a peptide[12]. The Apelin/APJ system has been studied in the context of lipid and glucose metabolism, regulation of blood pressure, body fluids, and several other processes[13],[14]. Some authors suggest that there is a relationship between apelin signaling and retinal angiogenesis [15]. Another study has reported an association between high apelin levels in serum and proliferative diabetic retinopathy [16].

2. MATERIALS AND METHODS

The present study was undertaken in the Department of Biochemistry in collaboration with the Department of ophthalmology, SPMCH&RI, Hosur, Tamil Nadu, India, from Dec 2023 to Dec 2025.

Study subjects and design

This was a case control study. Totally 110 healthy control, and 110 patients without DR and 110 patients with DR were recruited from the out-patient and in-patient facilities of the departments of Ophthalmology and Medicine. Participants were explained about the study protocol and written informed consent was obtained from them prior to participation in the study. Detailed ocular examination of all the participants was done, using dilated ophthalmoscopy and slit lamp bio microscopy, to look for diabetic retinopathy (DR). The patients were graded for DR according to International clinical diabetic retinopathy disease severity scale which is in accordance with "Early treatment diabetic retinopathy study (ETDRS) scale"[17]. The eye with a more severe form of retinopathy was used for the grading and grouping of the patients.

Inclusion criteria:

Type2 DM with retinopathy, Type2 DM without retinopathy, Type2 DM of >5years duration, Non-Diabetic Healthy Control, Age range:30-to-70-year, Sex: Male & Female were included in the study.

Exclusion criteria:

Age <30 and >70 years. Type1 DM T2DM patients with Nephropathy, Neuropathy, Angiopathy Chronic inflammatory diseases, Hypertension, Pregnancy, Chronic liver, pulmonary and kidney disease Previous ocular surgery and ocular tumours were excluded from the study

Study groups (110 patients each):

Group1:110 Type2 diabetes mellitus with retinopathy (DR)

Group2:110 Type2 diabetes mellitus without retinopathy (DNR)

Group3: 110 Healthy controls (HC)

Demographic and clinical data

Detailed information of all patients was recorded including age, gender and duration of diabetes (since the time of diagnosis).

Biochemical analysis

About 8 ml of blood sample were drawn from the patients, in that 5ml of blood sample collected in the plain tube without anticoagulant and after centrifugation; two aliquots of serum were separated. One tube was used to measure fasting serum glucose (FSG), Urea, Creatinine, Uric acid, Total protein, Albumin, ALT, Bilirubin, Total cholesterol (TC), triglycerides (TGL) and HDL-cholesterol (HDLC) using auto-analyzer (Diasys sys200) LDL-cholesterol (LDL-C) was calculated using Friedewald formula: LDL-C=TC -(HDLC+Triglyceride/ 5). The other tube containing serum sample were stored at -80 degree Celsius for the quantitative analysis of chemerin and apelin by ELISA method (Krishgen Biosystem),3ml of Blood sample in an EDTA tube was used for the estimation of HbA1c.

Statistical Analysis

The data obtained during the current study were analysed statistically using SPSS version 22.0 to determine the significance of the different parameters by one-way ANOVA, data represent mean ± SE; $P<0.05$ was considered as statistically significant

3. RESULT

Parameters	Healthy Control	T2DM Without DR	T2DM with DR	P-Value
FBS(mg/dl)	90.74±11.32	190.60±61.94	201.95±57.69	<0.01*
PPBS(mg/dl)	111.39±12.74	279.4±86.90	297.02±83.69	<0.01*
HbA1C	4.97±0.51	8.36±1.26	14.86±43.70	<0.01*
TC(mg/dl)	146.54±27.29	174.22±36.79	181.86±36.10	<0.01*
TGL(mg/dl)	119.68±25.57	138.49±35.94	151.76±57.05	<0.01*
HDL(mg/dl)	39.46±5.43	39.98±6.86	37.69±8.81	0.047
LDL(mg/dl)	76.8±16.26	86.22±23.67	88.60±29.20	<0.01*
VLDL(mg/dl)	24.92±6.14	27.44±7.26	30.60±11.85	<0.01*
Urea(mg/dl)	21.94±6.86	23±7.02	23.60±7.14	0.165
Creatinine(mg/dl)	0.83±0.19	0.84±0.21	0.86±0.22	0.450
Uric acid(mg/dl)	4.99±1.00	4.68±0.93	4.94±1.18	0.058
Bilirubin(mg/dl)	0.65±0.18	0.62±0.20	0.65±0.29	0.613
ALT(IU/L)	23.89±6.21	26.12±11.30	23.23±11.21	0.085
TP(g/dl)	7.01±0.66	6.91±0.67	6.91±0.79	0.482
ALB(g/dl)	4.32±0.69	4.51±2.98	3.98±0.35	0.079
Chemerin(ng/ml)	150.04±21.06	2467.74±1238.21	2602.37±1333.18	<0.01*
Apelin(pg/ml)	29.66±5.64	36.92±8.33	40.18±7.35	<0.01*

Table 1. Comparison of Biochemical Parameters and special parameters across Groups

Data presented as mean±standard deviation, Statistics: one-way ANOVA.

FBS: Fasting Blood Glucose; HbA1C: Glycated Hemoglobin; TC: Total Cholesterol; TGL: Triglycerides;HDL-C:Highdensity Lipoprotein cholesterol; LDL-C: Low Density Lipoprotein Cholesterol; VLDL: Very Lowdensity Lipoprotein; TyG: Tri Glyceride; TP:Total Protein; ALB: Albumin;ALT: Alanine transaminase. Statistically significant (*P < 0.05).

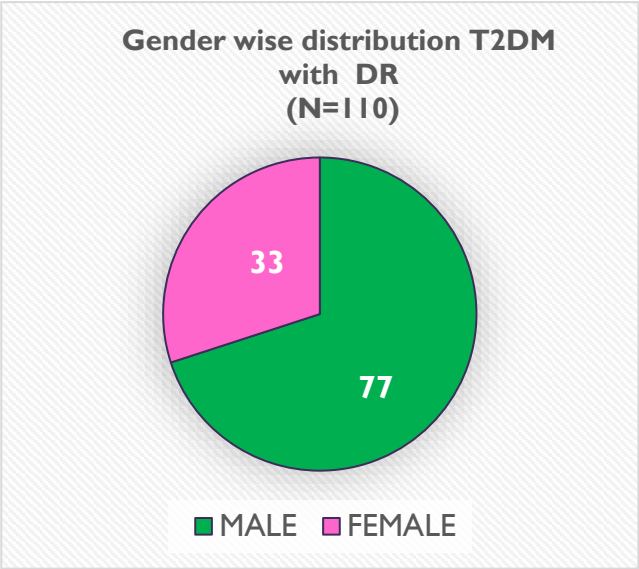

Fig1: Gender wise comparison of T2DM with Retinopathy (within cases)

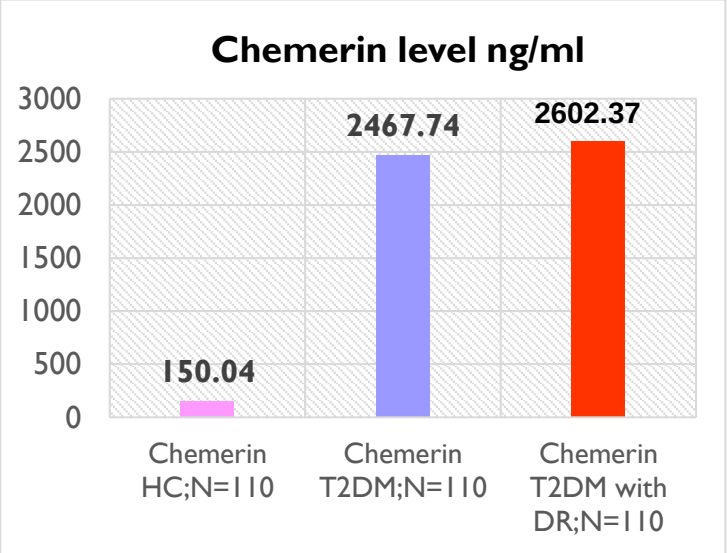

Fig:2, Comparison between special parameters of the study groups (Healthy Control, T2DM without Retinopathy & T2DM with Retinopathy)

Table 1 shows the biochemical characteristics of healthy control, T2DM patients with or without DR. We found a significant increase in Fasting serum glucose (FSG) Post Prandial blood glucose (PPBS), Glycated haemoglobin (Hba1c), Total cholesterol (TC), triglycerides (TGL) and HDL-cholesterol (HDL-C) LDL-Cholesterol, VLDL-Cholesterol, Chemerin and apelin in T2DM patients with DR group in comparison to T2DM patients without DR group and healthy control group. There was significant decrease in HDL-C level in DR group compared to T2DM without DR and HC group. There were no significant differences between the studied groups as regards serum Creatinine, Urea, and Uric acid, Total protein, Albumin, Bilirubin.

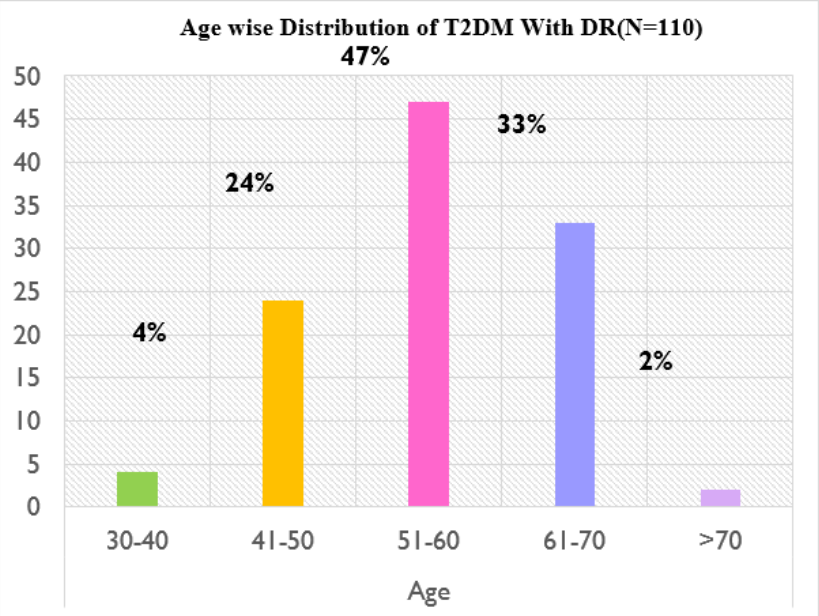

Fig:3, Age Wise Distribution of T2DM with Retinopathy (Within Cases)

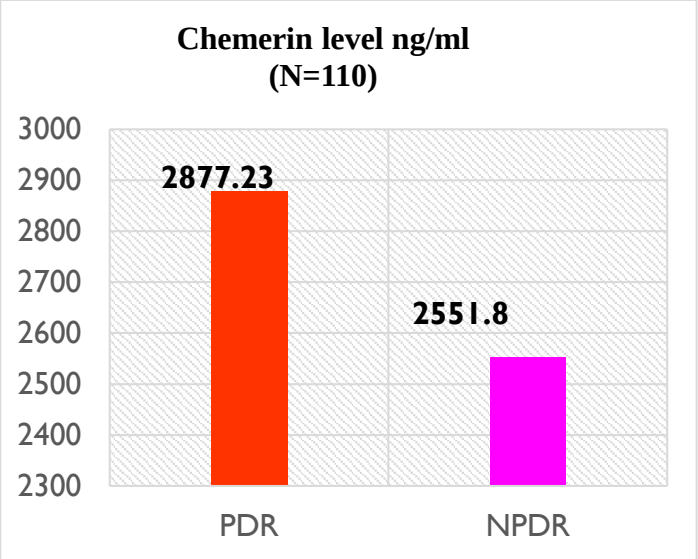

Fig 4: Comparison of Special Study Parameters Between PDR And NDPR Groups (Within Cases)

Fig1, out of 110 DR ,77 were males (70%) and 33 (30%) females. Fig2, Shows Serum chemerin level was significantly higher in group 1 than in group2 and group 3. Fig3, Age wise distribution of type 2 DM with DR, out of 110 DR,50 -60 age group peoples are more affected by DR when compare to other age group. Serum concentration of chemerin between NPDR and PDR group are presented in Fig 4, Serum chemerin was significantly higher in the PDR group compared with the other groups, in the NPDR group compared with the T2DM group and controls.

4. DISCUSSION

Serum chemerin levels were considerably greater in the diabetes groups than in the control groups in the current investigation. This is comparable to the findings of [11]., who found that patients with type 2 diabetes had significantly greater serum chemerin levels than people with normal glucose tolerance. The endocrine activity of adipose tissue appears to be intimately associated with type 2 diabetes. (e.g. chemerin) by adipocytes might cause a persistent inflammatory condition that may be a major factor in the development of type 2 diabetes and insulin resistance[18]. Additionally, some research has linked chemerin to inflammatory responses.

Chemerin can contribute to the development and spread of inflammation by promoting chemotaxis and macrophage adherence to extracellular matrix proteins[19]. Chemerin can activate nuclear factor-kB and mitogen-activated protein kinase pathways in a variety of inflammatory cells, including monocytes, macrophages, and immature dendritic cells[20], through the binding of Chemerin receptor 23 (ChemR23). These cells are crucial to the inflammatory process[21]. By controlling the amount of ChemR23 expression in vascular endothelial cells, chemerin also has a significant impact on these cells [22]. These suggest that the inflammatory state of vascular endothelial cells may be influenced by the Chemerin and ChemR23 system.

According to[23], chemerin plays a role in adipogenesis and inflammatory processes in diseases such as diabetes mellitus, metabolic syndrome, and cardiovascular problems. According to this study, the PDR group's serum chemerin level was noticeably higher than the NDR groups. According to several studies, apelin and chemerin both activate MAPKs and the PI3K/Akt pathways, which contribute to angiogenesis, neovascularization, and endothelial dysfunction [24 & 25]. The existence of several chemerin iso-forms with pleiotropic activities, as well as localized expression and activation, can be partially responsible for some of the contradictory results across different studies.

Overall, our research suggests that chemerin's involvement in inflammatory and angiogenic pathways may contribute to the pathophysiology of DR in individuals with type 2 diabetes. One of the reasons why working-age individuals have poor vision is DR. A key factor in the pathophysiology of DR is vascular endothelial dysfunction. Endothelial cell activities are impacted by growth factors, cytokines, hyperglycemia, and vasoactive substances[26]. The development of DR may also be impacted by chemerin, a newly identified adipocytokine that is linked to inflammation, neovascularization, and obesity[27].

According to [28], patients with PDR had higher amounts of vitreous chemerin than patients without DR. According to Du et al., patients with PDR had greater serum concentrations of chemerin than patients with NPDR. According to Tahir et al., the DM group had a greater serum chemerin level than the control group. According to their findings, elevated chemerin levels may increase oxidative stress, inflammation, insulin resistance, and angiogenesis factors, all of which may have a role in the pathophysiology of diabetic retinopathy [29].

In another set of trials, there was no discernible difference in serum chemerin levels between the control group and DM patients. There was no discernible change in serum chemerin level in healthy people than DM, according to Halawa et al. and Du et al. Comparing the groups with and without retinopathy, the retinopathy group had a significantly higher serum chemerin level. According to the authors of those research, increased chemerin levels may impact the pathophysiology of retinopathy by elevating hyperlipidemia, oxidative stress, and inflammation [28 & 29].

Apelin pertains to a bioactive peptide which functions in a number of emojis physiological and pathological conditions such as glucose homeostasis, angiogenesis, diabetes mell Bright and its complications. We in this study have found that serum apelin level in the PDR group is markedly higher than both NDR and NPDR groups. In a previous study conducted in the Chinese population, the researchers found serum apelin-13 level to be higher in NPDR compared to T2DM, but there was no significant difference between the level of NPDR and PDR groups. We also analyzed our data under the assumption that T2DM with retinopathy constitutes two groups, namely proliferative diabetic retinopathy PDR and NPDR. Here we find that serum apelin level is significantly higher in PDR group than rest. An animal study has reported that elevation of serum apelin level is a compensatory mechanism to sustain the insulin sensitivity state in conditions associated with insulin resistance such as DR.At the same time it is damaging in the eye tissues, and animal studies have demonstrated that the silencing of apelin expression results in decreased pathological angiogenesis due to the changing of proliferating endothelial cells to a more quiescent phenotype [30].

5. CONCLUSION

Our results indicate that chemerin and apelin level were significantly higher in type 2 diabetic patients with diabetic retinopathy compared to those without diabetic retinopathy and to the control group. The notable differences in chemerin and apelin, along with fasting blood sugar, total cholesterol, triglycerides and low-density lipoprotein suggest that elevated chemerin levels play a crucial role in the pathogenesis of diabetic retinopathy. This elevation is linked to increased inflammation, insulin resistance, oxidative stress, and factors promoting angiogenesis.

DISCLOSURE:

The authors declared no conflicts of interest.

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ETHICAL APPROVAL

The institute ethics committee of CARE approved this study (Ethics certificate No.: IHEC-II/0454/23).

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