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Research Article

STUDY THE EFFECT OF SERUM CHEMERIN IN TYPE II DIABETES MELLITUS PATIENTS WITH AND WITHOUT DIABETIC RETINOPATHY

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ABSTRACT

Objective: Diabetic retinopathy (DR) arises from oxidative stress, inflammation, and pro-angiogenic signaling. Chemerin, a pleiotropic adipokine, links adipogenesis, glucose homeostasis, and inflammatory pathways. This study aimed to quantify serum chemerin in type 2 diabetes mellitus (T2DM) with and without DR.

Methods: This was comparative cross-sectional study. Adults were grouped as healthy controls (n=110), T2DM without DR (n=110), and T2DM with DR (n=110). Serum chemerin was measured by enzyme-linked immunoassay. Group differences were assessed using one-way analysis of variance (ANOVA) with Tukey's HSD *post hoc* when assumptions were met or Games-Howell when variances were unequal. Within-DR staging (non-proliferative DR [NPDR] vs. proliferative DR [PDR]) used independent-samples tests.

Results: Chemerin differed significantly across groups (one-way ANOVA, $p<0.01$) and was higher in T2DM with DR than in T2DM without DR and controls. Mean±standard deviation chemerin concentrations were as follows: Controls 150.04±21.06 ng/mL; T2DM without DR 246.77±123.82 ng/mL; T2DM with DR 259.33±133.32 ng/mL. Pairwise Tukey's HSD comparisons were significant (all $p<0.05$). Within the DR cohort, serum chemerin was higher in PDR than NPDR (independent-samples t-test, $p<0.05$).

Conclusion: Elevated chemerin in DR supports adipokine-driven inflammation and angiogenesis in DR progression. Chemerin may aid risk stratification alongside glycemic and lipid indices, reinforcing the importance of early T2DM control and DR screening.

Keywords: Chemerin, Type 2 diabetes mellitus, Diabetic retinopathy, Adipokine, Angiogenesis.

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by impaired insulin secretion and peripheral insulin resistance, resulting in sustained hyperglycemia and multisystem complications. Diabetic retinopathy (DR) is a major microvascular complication of T2DM and a leading cause of vision loss when not detected and treated promptly [1]. People with T2DM have a substantially higher risk of DR than those without diabetes, underscoring the need for early intervention and regular screening [2,4]. Globally, DR contributes heavily to visual morbidity; pooled estimates highlight its high prevalence and multifactorial risk profile [3,4]. Clinically, diabetic macular edema frequently reduces visual acuity [5], and progression to proliferative DR (PDR) is associated with severe sequelae, including vitreous hemorrhage and profound visual impairment [6,7]. DR often coexists with glaucoma and cataract, compounding visual disability [4], and imposes psychosocial burdens that diminish quality of life [8].

In the search for biomarkers that mirror the underlying inflammatory and angiogenic processes of DR, adipokines, particularly chemerin, have emerged as strong candidates. This focus extends the epidemiological burden of DR by interrogating a plausible molecular signal that may track diabetes-related microvascular injury. Particularly, prior evidence for chemerin in DR has been mixed: several studies report higher serum or vitreous chemerin in DR and in PDR versus non-proliferative DR (NPDR) [9,10], yet heterogeneity in study design, biospecimen (serum vs. vitreous), and assay characteristics has produced variable results. Nevertheless, a meta-analysis indicates higher circulating chemerin in DR compared with diabetes without DR, supporting its potential as a biomarker of DR presence and severity [11].

Chemerin (initially identified as TIG2) is a pleiotropic adipokine that signals primarily via CMKLR1 (ChemR23) and also interacts with GPR1 and CCRL2 [9,11]. Secreted as an inactive precursor (prochemerin), it requires proteolytic activation to exert chemotactic effects on immune cells and to modulate adipocyte function; these properties link chemerin to inflammatory tone, adipogenesis, glucose metabolism, and insulin action central to T2DM pathophysiology [9-13]. Elevated circulating chemerin has been associated with obesity, features of the metabolic syndrome, and vascular dysfunction [14-18], while chemerin/CMKLR1 signaling is expressed in endothelial cells with angiogenic effects relevant to DR biology [17,19]. Together, these data provide biological plausibility for evaluating circulating chemerin as a candidate biomarker in T2DM with and without DR, while recognizing the need to clarify its incremental value amid mixed prior literature [19-23].

METHODS

Study setting

This investigation was conducted in the Department of Biochemistry, in collaboration with the Department of Ophthalmology, at St. Peter's Medical College Hospital and Research Institute (SPMCH&RI), Hosur, Tamil Nadu, India. Ethics: The protocol was approved by the Institutional Ethics Committee of Chettinad Academy of Research and Education (IHEC-II/0454/23). The study adhered to the principles of the Declaration of Helsinki, and written informed consent was obtained from all participants before enrolment.

Study design and participants

This was a comparative cross-sectional study. Participants were recruited from the outpatient and inpatient services of the Departments of Ophthalmology and Medicine and stratified into three groups: Healthy controls (HC, n=110), T2DM without DR (DNR, n=110), and T2DM with DR (DR, n=110). All participants underwent comprehensive ocular evaluation, including dilated ophthalmoscopy and slit-lamp biomicroscopy. DR severity was graded according to the International Clinical DR Disease Severity Scale aligned with ETDRS criteria [12]. For grading and group allocation, the eye with the more severe retinopathy determined the patient's stage.

Inclusion criteria

Adults aged 30–70 years of either sex were eligible if classified as: (i) non-diabetic HC; (ii) T2DM without retinopathy; or (iii) T2DM with retinopathy. A diabetes duration >5 years was required for the diabetic groups.

Exclusion criteria

Exclusions included: age <30 or >70 years; type 1 diabetes; T2DM with nephropathy, neuropathy, or clinically evident macro/micro-angiopathy; chronic inflammatory diseases; hypertension; pregnancy; chronic hepatic, pulmonary, or renal disease; prior ocular surgery; and ocular tumors.

Sample size justification

An a priori power analysis for a one-way analysis of variance (ANOVA) (three groups) with α=0.05, power (1–β)=0.90, and a small-to-moderate effect size (f=0.20) indicated a minimum total sample of ≈246 (~82 per group). We enrolled n=330 (110 per group), exceeding the calculated requirement to ensure adequate power for between-group comparisons of chemerin.

Demographic and clinical data

Age, sex, and diabetes duration (years since diagnosis) were recorded.

Biochemical analyses

After an overnight fast, 8 mL of venous blood was collected. For clinical chemistry, 5 mL was transferred to a plain tube, allowed to clot, and centrifuged; serum was analyzed for fasting glucose (reported as FPG in tables), urea, creatinine, uric acid, total protein (TP), albumin (ALB), alanine aminotransferase (ALT), total cholesterol (TC), triglycerides (TG), high-density lipoprotein-cholesterol (HDL-C), and very-low-density lipoprotein-cholesterol (VLDL-C) on an automated analyzer (Diasys SYS200). Low-density lipoprotein-cholesterol (LDL-C) was calculated by the Friedewald formula (LDL-C = TC − [HDL-C + TG/5]) when TG <400 mg/dL; otherwise, LDL-C was not calculated. For post-prandial blood sugar, a separate venous specimen was drawn 2 h after the participant's principal meal and processed on the same analyzer. For hemoglobin A1C (HbA1c), 3 mL was collected into ethylenediaminetetraacetic acid tubes and measured by ion-exchange high-performance liquid chromatography.

For chemerin, an aliquot of serum was stored at −80°C (single freeze-thaw) until analysis. Serum chemerin was quantified using a sandwich enzyme-linked immunoassay (ELISA) (GENLISA™ Human Chemerin ELISA-high Sensitivity, Krishgen Biosystems, India; catalog/SKU: KBH2070) according to the manufacturer's instructions. All chemerin concentrations are reported in ng/mL. Calibrators supplied with the kit were run in duplicate on each plate, and a 4-parameter logistic (4-PL) curve was used for interpolation. Samples outside the validated dynamic range were diluted and re-assayed to fall within the linear range. Each sample was assayed in duplicate; plates were accepted if duplicate CV ≤10% and the standard-curve R^2 ≥0.99. According to the manufacturer's GENLISA platform specifications, intra-assay CV <10% and inter-assay CV <12%, we verified plate-level precision against these thresholds in test runs.

Table 1: Descriptive data of the study groups

Characteristic	Healthy controls (HC)	T2DM without retinopathy (DNR)	T2DM with retinopathy (DR)
Number (M/F)	110 (62/48)	110 (79/31)	110 (77/33)
Age (years)	53.97±10.50	54.33±8.90	56.58±8.67
Duration of diabetes (years)	—	6.60±3.68[a]	9.22±3.68[b]

Age did not differ significantly across groups. Diabetes duration was longer in DR versus DNR ([a] vs. [b]; *P*<0.05; tested between diabetic groups only)

Blinding

To minimize measurement bias, laboratory personnel performing the chemerin ELISA were blinded to clinical group assignments. Serum aliquots carried coded identifiers with group labels concealed until after data lock.

Statistical analysis

Data are presented as mean±standard deviation unless otherwise specified. Assumption checks included Shapiro-Wilk for normality and Levene's test for homogeneity of variances. Primary comparison (HC vs. DNR vs. DR): One-way ANOVA with Tukey's HSD *post-hoc* where assumptions were met; if variances were unequal, Welch's ANOVA with Games-Howell *post hoc*; if non-normal, Kruskal-Wallis with Dunn-Bonferroni *post hoc*. Within-DR staging (NPDR vs. PDR): Independent-samples t-test (or Mann-Whitney U if non-normal). Two-sided p<0.05 was considered statistically significant. Analyses were performed in the Statistical Package for the Social Sciences v22.0.

RESULTS

Participant characteristics

A total of 330 participants were included: HC (HC, n=110), T2DM without DR (DNR, n=110), and T2DM with DR (DR, n=110). Absence of DR in the DNR group was defined by the lack of macular edema, hard exudates, blot hemorrhages, microaneurysms, cotton-wool spots, and neovascularization. Within the DR cohort, severity was classified as NPDR or PDR according to the International Clinical DR Disease Severity Scale aligned with ETDRS criteria (Table 1) [12].

Biochemical profile across groups

Group-wise comparisons (HC vs. DNR vs. DR) followed the prespecified plan. Where assumptions were met, one-way ANOVA with Tukey's HSD was used; with unequal variances, Welch's ANOVA with Games-Howell; if non-normal, Kruskal-Wallis with Dunn-Bonferroni. FPG, PPBS, HbA1c, TC, TG, LDL-C, VLDL-C, and chemerin (ng/mL) were higher in DR versus DNR and HC, while HDL-C was lower in DR. Urea, creatinine, uric acid, TP, ALB, bilirubin, and ALT did not differ significantly (Table 2).

Chemerin by DR subtype

Within the DR cohort, serum chemerin was significantly higher in PDR than NPDR (independent-samples t-test; p<0.05), consistent with a gradient of inflammatory/angiogenic activity alongside DR severity [12].

DISCUSSION

Principal findings

It observed a clear gradient in circulating chemerin: Levels were higher in T2DM than in controls and highest in T2DM with DR, with an additional within-case rise from NPDR to PDR (overall between-group testing p<0.01; *post hoc* contrasts p<0.05; NPDR vs. PDR p<0.05). These magnitudes fall within ranges commonly reported for adults with diabetes and are biologically plausible when expressed and assayed in ng/mL using a validated dynamic range. As specified a priori, variance heterogeneity for chemerin was handled with Welch's ANOVA and Games-Howell *post hoc*, and the pattern of results remained directionally consistent with standard ANOVA/Tukey contrasts. Taken

Table 2: Comparison of biochemical parameters across groups

Parameter	Healthy controls (HC)	T2DM without DR (DNR)	T2DM with DR (DR)	p-value	Test/*post-hoc* note
FPG (mg/dL)	90.74±11.32[a]	190.60±61.94[b]	201.95±57.69[b]	<0.01	ANOVA/Tukey: DNR=DR>HC
PPBS (mg/dL)	111.39±12.74[a]	279.40±86.90[b]	297.02±83.69[b]	<0.01	ANOVA/Tukey: DNR=DR>HC
HbA1c (%)	4.97±0.51[a]	8.36±1.26[b]	9.16±1.37[c]	<0.01	ANOVA/Tukey: DR>DNR>HC[†]
TC (mg/dL)	146.54±27.29[a]	174.22±36.79[b]	181.86±36.10[b]	<0.01	ANOVA/Tukey: DNR=DR>HC
TG (mg/dL)	119.68±25.57[a]	138.49±35.94[b]	151.76±57.05[b]	<0.01	Welch/Games-Howell: DNR=DR>HC
HDL-C (mg/dL)	39.46±5.43[a]	39.98±6.86[a]	37.69±8.81[b]	0.047	ANOVA/Tukey: DR<HC=DNR[‡]
LDL-C (mg/dL)	76.80±16.26[a]	86.22±23.67[b]	88.60±29.20[b]	<0.01	ANOVA/Tukey: DNR=DR>HC
VLDL-C (mg/dL)	24.92±6.14[a]	27.44±7.26[b]	30.60±11.85[b]	<0.01	Welch/Games-Howell: DNR=DR>HC
Urea (mg/dL)	21.94±6.86	23.00±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[a]	246.77±123.82[b]	259.33±133.32[c]	<0.01	Welch/Games-Howell: DR>DNR>HC[§]

[†]HbA1c SD for DR corrected (typographical error in the original table). [‡]Although the overall test was significant (P=0.047), the mean difference was small; the contrast was driven by lower HDL-C in DR versus the other groups. [§]Unit correction: Chemerin values are expressed in ng/mL throughout. HC: Healthy controls, DNR: T2DM without diabetic retinopathy, DR: T2DM with diabetic retinopathy, FPG: Fasting plasma glucose, PPBS: Post-prandial blood sugar, TC: Total cholesterol, TG: Triglycerides, LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol, VLDL-C: Very-low-density lipoprotein cholesterol, TP: Total protein, ALB: Albumin, ALT: Alanine aminotransferase, ANOVA: Analysis of variance

together, these findings support an association between increasing chemerin and both the presence and severity of DR in T2DM.

Context with prior evidence

Chemerin has repeatedly been linked to T2DM and insulin resistance, reflecting adipose-tissue endocrine activity and low-grade inflammation [11,13,15-18]. Studies focused on eye disease report higher vitreous and/or serum chemerin in DR, frequently with a step-up in PDR compared with NPDR, although results are not entirely uniform across cohorts and assay platforms [23-25]. A meta-analysis similarly found higher circulating chemerin in DR versus diabetes without DR, lending quantitative support to a DR-specific signal beyond diabetes alone [21]. Our results align with this pattern and, by standardizing reporting in ng/mL, facilitate cross-study comparability, and reduce a common source of heterogeneity in the literature.

Biological plausibility

Mechanistically, chemerin (TIG2) is secreted as prochemerin and requires proteolytic activation before signaling primarily through CMKLR1 (ChemR23), with additional interactions at GPR1 and CCRL2 [9,11]. Chemerin recruits and activates innate immune cells, enhances macrophage adhesion, and can engage NF-κB and MAPK pathways, key axes in chronic inflammation relevant to diabetic microangiopathy [14-16]. Endothelial expression of ChemR23 and chemerin-driven angiogenic responses provide a vascular conduit linking metabolic inflammation to microvascular injury pertinent to DR [17,19]. These pathways, together with hyperglycemia-induced oxidative stress, offer a coherent explanation for the graded rise of chemerin with DR severity [22]. Importantly, isoform-specific activation and local protease activity may modulate bioactive chemerin fractions, potentially influencing tissue-circulation correlations in DR.

Clinical implications

While chemerin is not yet ready for stand-alone clinical decision-making in DR, our data suggest potential risk-stratification value alongside established indices (e.g., HbA1c and lipids). In practical terms, a higher chemerin level could flag an inflammatory/angiogenic milieu associated with DR presence or progression and justify closer retinal surveillance. However, no universally accepted clinical cutoffs or calibration standards exist, and incremental predictive utility (e.g., AUC improvement or reclassification beyond conventional factors) requires prospective testing. Future work should evaluate whether adding chemerin to multivariable models or AI-assisted retinal image analytics improves decision thresholds and yields measurable net benefit in screening workflows.

Strengths

Key strengths include ETDRS-aligned grading, enhancing phenotypic accuracy [12]; a large, balanced sample across three groups; pre-specified assumption checks with appropriate *post-hoc* procedures, and laboratory blinding to minimize measurement bias. These elements directly address common methodological sources of variability and support the internal validity of the observed gradients in chemerin.

Limitations

This cross-sectional, single-center study cannot infer causality and may be susceptible to residual confounding (e.g., adiposity measures, medications, renal function within normal ranges, and broader inflammatory status). Chemerin was measured once, and isoform-specific or receptor-level profiling (CMKLR1/GPR1/CCRL2) was not performed; vitreous levels and parallel inflammatory/adipokine panels were not assessed [11,13-21]. Although the overall sample was large, within-DR staging analyses (NPDR vs. PDR) reduce effective power for subgroup contrasts, and potential batch or matrix effects cannot be fully excluded despite stringent QC. Future research should include longitudinal, multi-center cohorts with serial serum/vitreous chemerin, pre-specified adjustment for metabolic/vascular covariates, and mechanistic readouts (e.g., NF-κB/MAPK/PI3K-Akt), alongside formal evaluation of incremental predictive value and clinical utility for DR screening and progression [21-25].

CONCLUSION

Circulating chemerin was significantly higher in T2DM than in controls and highest in T2DM with DR, with an additional rise in PDR versus NPDR. These results, consistent with mechanistic and epidemiological evidence, support chemerin as a plausible biomarker linking metabolic inflammation to retinal microvascular disease in diabetes. Clinically, chemerin may complement established risk markers to prioritize surveillance, but prospective validation, standardized assays, thresholds, and demonstration of incremental predictive utility and net clinical benefit are required before routine adoption.

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CONFLICTS OF INETEREST

The authors declared no conflicts of interest.

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ETHICAL STATEMENTS

The study was approved by the Institutional Ethics Committee of Chettinad Academy of Research and Education (IHEC-II/0454/23). Permission to recruit at St. Peter's Medical College Hospital and Research Institute, Hosur, was obtained prior to enrolment. Written informed consent was taken from all participants.

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