https://doi.org/10.48047/AFJBS.6.14.2024.4406-4416

African Journal of Biological Sciences

Journal homepage: http://www.afjbs.com

Research Paper Open Access

Meta-Analysis of Chemerin Levels in Type II Diabetic Patients with Retinopathy

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Volume 6, Issue 14, Aug 2024

Received: 09 June 2024

Accepted: 19 July 2024

Published: 12 Aug 2024

doi: 10.48047/AFJBS.6.14.2024.4406-4416

Abstract

Background: Diabetes Mellitus (DM) 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 pro-angiogenic cytokines. Chemerin, an adipokine influencing adipogenesis and lipid metabolism, plays a crucial role in metabolic syndrome by regulating inflammatory processes in adipose tissue.

Aim : The study aimed to evaluate the influence of serum chemerin levels in type 2 diabetes patients with diabetic retinopathy.

Methodology: Meta-analysis was conducted on 14 published studies investigating serum chemerin levels in patients with type 2 diabetes mellitus (T2DM) with and without DR as control group. A random-effects REML model was used to estimate the pooled mean of serum chemerin levels across these studies.

Results: After screening, 14articles were included in the meta-analysis including820 DR cases and 709cases without DR. Based on our meta-analysis, the combined average level of serum chemerin among T2DM patients with DR was 375.32 ±100.94 ng/ml, exceeding that found in T2DM patients without DR (296.47±81.73 ng/ml).Chemerin levels in patients with DRwere significantly higher than those in the group without DR[SMD: 1.19, 95% CI (0.63,1.76)] with p value 0.0005.

Conclusion: The meta-analysis indicated a notable association between T2DM with DR and serum chemerin levels. These results also recommend that regular assessment of serum chemerin could aid in managing T2DM effectively.

Keywords: *T2DM, DR, Chemerin.*

Introduction

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by insulin resistance and impaired insulin secretion, leading to elevated blood glucose levels. This condition presents a significant global health burden due to its increasing prevalence and associated complications, such as diabetic retinopathy (DR). Diabetic retinopathy is a

common microvascular complication of T2DM, affecting the retina and potentially causing vision loss if untreated (Wong*et al.,* 2016). Recent research underscores the strong association between T2DM and diabetic retinopathy.Sabanayagam *et al.* (2019) highlighted that individuals with T2DM have a significantly higher risk of developing diabetic retinopathy compared to those without diabetes, emphasizing the importance of regular screening and early intervention.According to the International Diabetes Federation (IDF), the global prevalence of diabetes mellitus (DM) was estimated to be 463 million in 2019 and is projected to reach 700 million by 2045. Diabetic retinopathy continues to be a prevalent complication of DM and remains a significant cause of avoidable blindness among adults in the working-age population (Teo *et al.* 2021).
Recent research underscores the detrimental effects of diabetic retinopathy (DR), a leading cause of vision impairment and blindness among individuals with diabetes globally. Yau *et al.* (2012) emphasizes its widespread prevalence and associated risk factors, highlighting its profound impact on vision loss. Korobelnik *et al.* (2014) discussed that macular edema, a common complication of DR characterized by fluid accumulation in the macula, which significantly affects visual acuity. Advanced stages of DR can progress to proliferative diabetic retinopathy (PDR), potentially leading to complications such as vitreous haemorrhage, further exacerbating vision impairment (Wykoff, 2024). Moreover, individuals with DR are at heightened risk for developing conditions like glaucoma and cataracts (Zhang *et al.* 2008). The psychosocial consequences of DR are also noteworthy, impacting patients' quality of life through compromised vision-specific function and psychological well-being (Cooper *et al*., 2020). Collectively, these studies underscore the multifaceted and profound impact of DR, emphasizing the critical need for effective management and treatment strategies to mitigate its effects on visual health and overall well-being.Hence, timely intervention in the management of diabetes with DR is extremely important.

In addition to being an important source of energy, adipose tissue secretes a number of adipokines (adipocytokines), such as adiponectin, leptin, apelin, chemerin, and omentin-1. Numerous functions of these adipokines include inflammation, metabolic control, and the pathogenesis of metabolic diseases like obesity, insulin resistance, and cardiovascular disease. Because of their involvement in insulin resistance and the pathogenesis of T2DM, adipokines have been thoroughly researched in relation to diabetes. For metabolic health, adiponectin in TD2M promotes fatty acid oxidation and glucose absorption (Weyer *et al.,* 2001). In contrast, increased levels of leptin in obese individuals can exacerbate insulin function and cause resistance (Zhang *et al.,* 1994).

Chemerin, initially identified as TIG2 in the late 1990s during studies on retinoids' effects on skin cells, was later found in 2003 to be a ligand for the G-protein coupled receptor CMKLR1 (Wittamer *et al.,* 2004), linking it to the chemokine family and revealing its role in immune cell migration to inflammation sites. Chemerin is synthesized as a precursor protein, prochemerin, which becomes active and binds to CMKLR1, influencing immune responses and metabolic processes like adipocyte differentiation, glucose metabolism, and insulin sensitivity (Bozaoglu *et al.,* 2007), thus linking it to obesity and T2DM. It interacts with receptors GPR1 and CCRL2, affecting energy homeostasis across tissues. Elevated chemerin levels are associated with metabolic disorders, cardiovascular diseases, and inflammation, making it a potential biomarker and therapeutic target (Rourke *et al.,* 2013).Furthermore, the association between chemerin and diabetic retinopathy (DR) remains debated. The lack of a systematic review and meta-analysis in this specific area could potentially misguide physicians in choosing appropriate procedures for relevant conditions.Therefore, this meta-

analysis study is aimed to evaluate theassociation between chemerin with TD2M with and without and DR.

Methodology

Cochrane library, Embase,EBSCO, Google Scholar, PubMed, SCOPUS, Web of Science and Willy databases were used to search for potential studies. Appropriate keywords such asDiabetes mellitus, T2DM, diabetic retinopathyandDRin combination with chemerin.. The search period was from 2000 to 2024. We simultaneously traced the references of the collected relevant literature, searched for studies that met the inclusion criteria, and eliminated duplicate studies. This meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Page *et al.,* 2021).

Inclusion criteria

Only published studies that met the following criteria were included inthis meta-analysis: a) studies in english language, b) studies with T2DM patients with DR, c) studieswith T2DM patients without DR, d) studies with corelation between chemerin levels and DR and e) studies with not <20 T2DM patients.

Exclusion criteria

(1) Duplicate publications, (2) Review studies and (3) Animal studies.

Data review and extraction

Research articles meeting the specified inclusion and exclusion criteria were independently reviewed by two expert reviewers. In cases where discrepancies arose, a third reviewer made the final decision. Data extracted from each study included the primary author's name, publication year, study period, region, number of patients with and without diabetic retinopathy (DR), as well as the mean and standard deviation of serum chemerin levels. The quality of the studies was assessed using the Newcastle-Ottawa Scale (NOS), which evaluates selection criteria, comparability, and outcome assessment, following guidelines from the Cochrane collaboration (Wells *et al*., 2000).

Statistical analysis

The study data were randomly generated using a random-effects model (REML) to analyze the standardized mean difference (SMD). The SMD was computed using Cohen’s d method with the restricted maximum-likelihood estimator to aggregate effect sizes across studies. Additionally, heterogeneity among studies was evaluated using Cochran’s Q-test and quantified using the I^2 statistic. The entire statistical analysis was carried out in the meta-analysis software R [version 3.6.0] (Pan *et al*., 2021).

Results

A total of 1160 studies were retrieved from search engines, and after screening, 14 articles were included in the meta-analysis (Fig. 1). These 14 articles encompassed 820TD2M cases with DRand 709 cases without DR. The characteristics of the selected studies are summarized in Table 1. Overall, the studies included in this meta-analysis were of acceptable quality according to the suggested criteria for the Selection, Comparability, and Exposure categories of the Newcastle-Ottawa Scale.

Fig. 1: PRISMA 2020 flow chart of studies included in meta-analysis

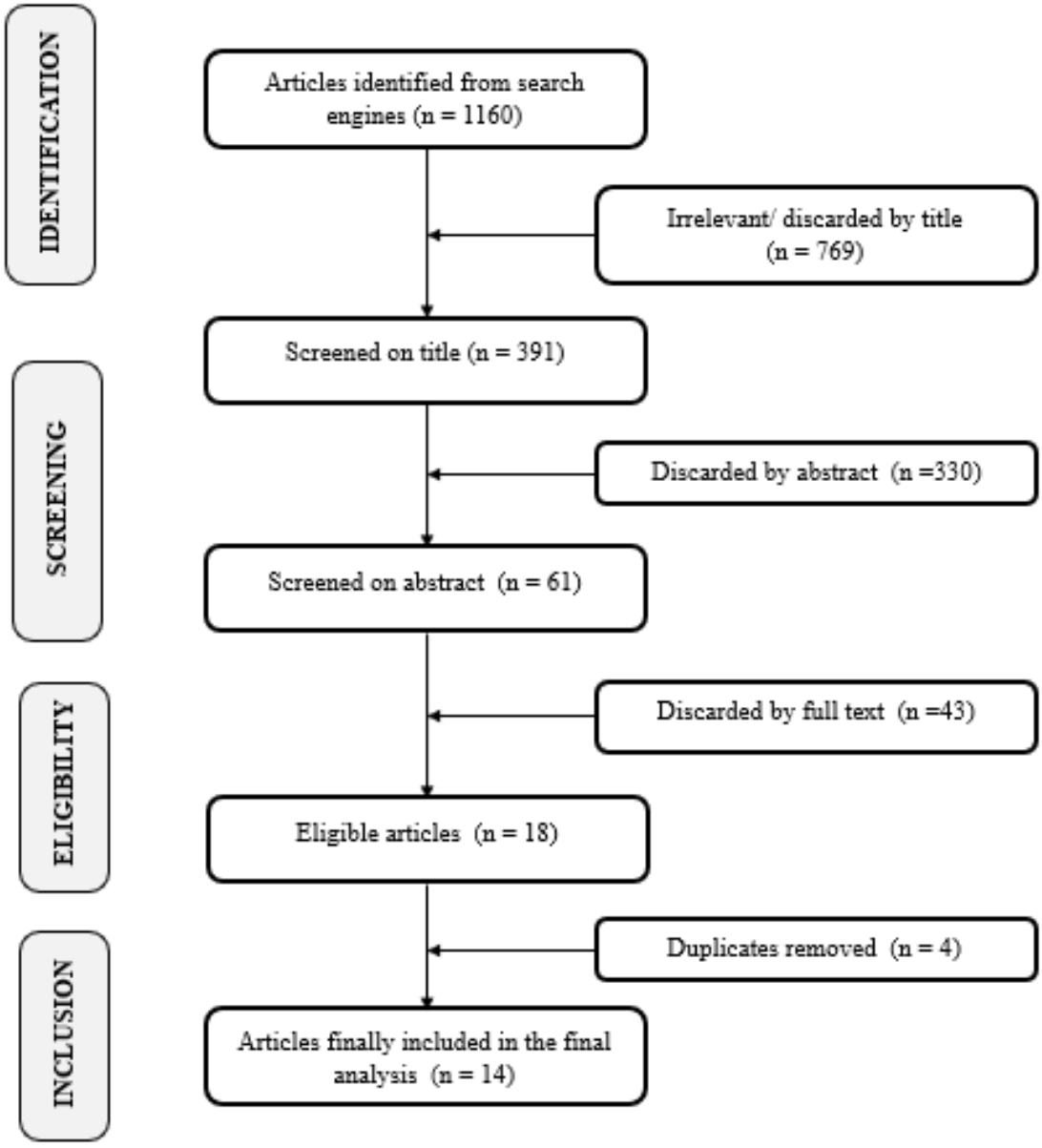


Table 1. Details of the studies included in meta-analysis

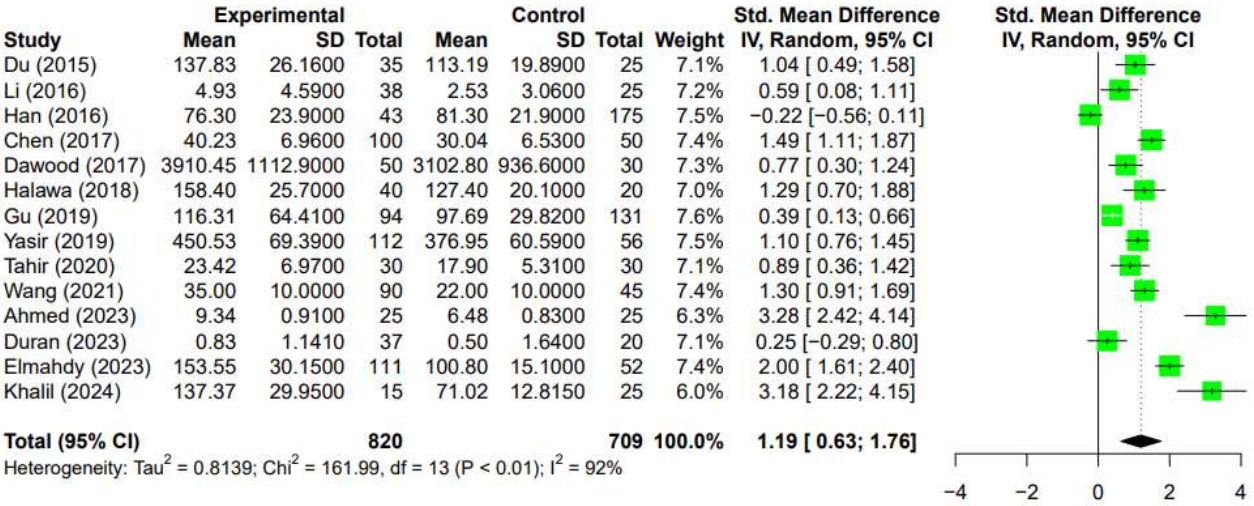
S.no.	Author	Year	Study period	Region	T2DM with DR*(experimental)*			T2DM without DR*(control)*		
					n	Chemerin(ng/ml)		n	Chemerin (ng/ml)	
						Mean	SD		Mean	SD
1	Du	2015	May 2012 - Apr 2013	China	35	137.83	26.16	25	113.19	19.89

2	Li	2016	-	China	38	4.93	4.59	25	2.53	3.06
3	Han	2016	-	Korea	43	76.3	23.9	175	81.3	21.9
4	Chen	2017	Jan 2014 - Dec 2016	China	100	40.23	6.96	50	30.04	6.53
5	Dawood	2017	Jan - Sep 2016	Egypt	50	3910.45	1112.9	30	3102.8	936.6
6	Halawa	2018	Janu-April 2018	Egypt	40	158.4	25.7	20	127.4	20.1
7	Gu	2019	Oct 2014 - Feb 2017	China	94	116.305	64.41	131	97.69	29.82
8	Yasir	2019	Aug2016 - Mar 2018	India	112	450.53	69.39	56	376.95	60.59
9	Tahir	2020	Jan - Sep 2020	Iraq	30	23.42	6.97	30	17.9	5.31
10	Wang	2021	-	China	90	35	10	45	22	10
11	Ahmed	2023	Dec 2021 - Apr 2022	Iraq	25	9.34	0.91	25	6.48	0.83
12	Duran	2023	-	Turkey	37	0.835	1.141	20	0.5	1.64
13	Elmahdy	2023	May 2020 - Jun 2021	Egypt	111	153.55	30.15	52	100.8	15.1
14	Khalil	2024	Dec 2022 - Jun 2023	Iraq	15	137.37	29.95	25	71.022	12.815

T2DM – Type 2 Diabetes Mellitus; DR – Diabetic Retinopathy; n – Number of patients;SD – Standard Deviation.

The meta-analysis data revealed that, the combined average level of serum chemerin among T2DM patients with DR was 375.32 ±100.94 ng/ml, exceeding that found in T2DM patients without DR (296.47±81.73ng/ml).The results of the meta-analysis demonstrated that the chemerin levels in patients with DR were significantly higherthan those in non-DR patients DR [SMD: 1.19, 95% CI (0.63, 1.76)] with p value 0.0005(P <0.01), as illustrated in the forest plots (Fig. 2). The heterogeneity or the Tau^2, the between study variance is 0.8139, indicates a positive association between the variables (chemerin levels) and I^2 value of 92% demonstrates considerable heterogeneity with Chi^2 value of 161.99 and degrees of freedom, 13.

Fig.2. Forest plots of chemerin levels in patients with DR (experimental) and without DR (control)



Study	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Du (2015)	137.83	26.1600	35	113.19	19.8900	25	7.1%	1.04 [0.49; 1.58]
Li (2016)	4.93	4.5900	38	2.53	3.0600	25	7.2%	0.59 [0.08; 1.11]
Han (2016)	76.30	23.9000	43	81.30	21.9000	175	7.5%	−0.22 [−0.56; 0.11]
Chen (2017)	40.23	6.9600	100	30.04	6.5300	50	7.4%	1.49 [1.11; 1.87]
Dawood (2017)	3910.45	1112.9000	50	3102.80	936.6000	30	7.3%	0.77 [0.30; 1.24]
Halawa (2018)	158.40	25.7000	40	127.40	20.1000	20	7.0%	1.29 [0.70; 1.88]
Gu (2019)	116.31	64.4100	94	97.69	29.8200	131	7.6%	0.39 [0.13; 0.66]
Yasir (2019)	450.53	69.3900	112	376.95	60.5900	56	7.5%	1.10 [0.76; 1.45]
Tahir (2020)	23.42	6.9700	30	17.90	5.3100	30	7.1%	0.89 [0.36; 1.42]
Wang (2021)	35.00	10.0000	90	22.00	10.0000	45	7.4%	1.30 [0.91; 1.69]
Ahmed (2023)	9.34	0.9100	25	6.48	0.8300	25	6.3%	3.28 [2.42; 4.14]
Duran (2023)	0.83	1.1410	37	0.50	1.6400	20	7.1%	0.25 [−0.29; 0.80]
Elmahdy (2023)	153.55	30.1500	111	100.80	15.1000	52	7.4%	2.00 [1.61; 2.40]
Khalil (2024)	137.37	29.9500	15	71.02	12.8150	25	6.0%	3.18 [2.22; 4.15]
Total (95% CI)			**820**			**709**	**100.0%**	**1.19 [0.63; 1.76]**

Heterogeneity: $Tau^2 = 0.8139$; $Chi^2 = 161.99$, df = 13 (P < 0.01); $I^2 = 92\%$

Square boxes represent the SMDs at 95% CI. SMD: standardized mean difference; CI, confidence interval.

The precision (study error) and results (SMD) of the individual studies were illustrated in the funnel plot (Fig.3).The outer dashed lines mark where about 95% of studies would lie without biases or heterogeneity. The vertical dashed line represents no intervention effect. The distribution shows symmetric visual characteristics, confirmed by a p-value > 0.05Egger's tests performed in our meta-analysis, demonstrated lesser publication bias with a p value of 0.0478 (Fig.4). An intercept with p >0.05suggests no publication bias (Lin and Chu, 2018).The lesser publication bias in our study can attributed to the limited number of available studies of chemerin level in T2DM with DR (Pan *et al*., 2021). The summary of the meta-analysis is illustrated in Fig.4.5.

Fig.3. Funnel plot of individual studies with their P values.

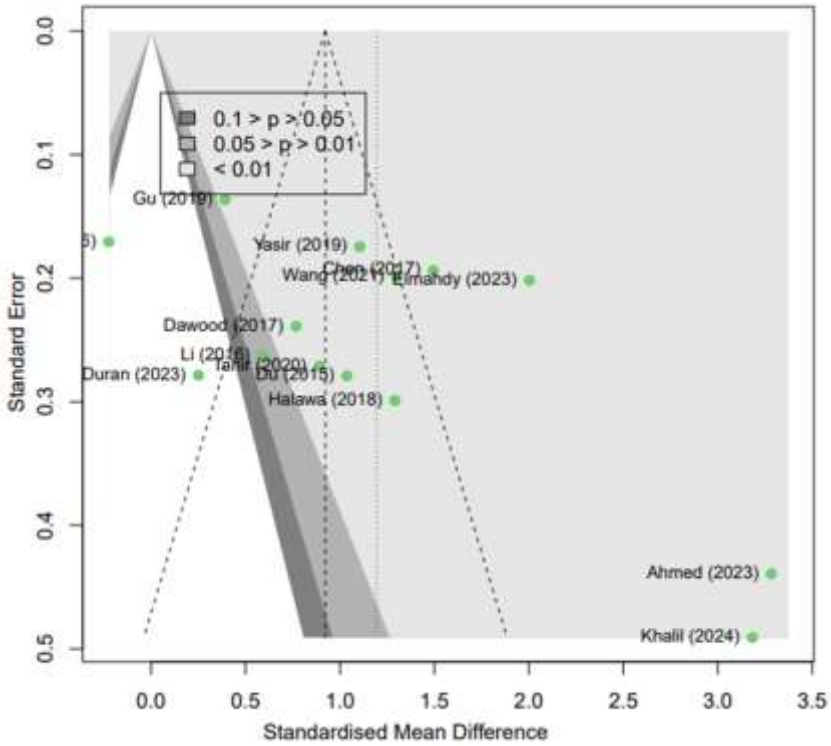


Fig.4. Egger's regression analysis of Publication bias

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Review:     Model: SMD - Random Effect

Linear regression test of funnel plot asymmetry

Test result: t = 2.20, df = 12, p-value = 0.0478

Sample estimates:
   bias se.bias intercept se.intercept
 5.9605  2.7049   -0.3261       0.5953

Details:
- multiplicative residual heterogeneity variance (tau^2 = 9.6105)
- predictor: standard error
- weight:    inverse variance
- reference: Egger et al. (1997), BMJ
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Fig.4.5. Summary of the meta-analysis

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Review:     Model: SMD -Random Effect

                   SMD            95%-CI %W(common) %W(random)
Du (2015)       1.0367 [ 0.4898; 1.5837]        4.4        7.1
Li (2016)       0.5915 [ 0.0759; 1.1071]        5.0        7.2
Han (2016)     -0.2242 [-0.5585; 0.1101]       11.9        7.5
Chen (2017)     1.4940 [ 1.1142; 1.8738]        9.2        7.4
Dawood (2017)   0.7686 [ 0.3001; 1.2371]        6.1        7.3
Halawa (2018)   1.2911 [ 0.7050; 1.8773]        3.9        7.0
Gu (2019)       0.3926 [ 0.1251; 0.6600]       18.6        7.6
Yasir (2019)    1.1048 [ 0.7626; 1.4469]       11.4        7.5
Tahir (2020)    0.8909 [ 0.3594; 1.4224]        4.7        7.1
Wang (2021)     1.3000 [ 0.9095; 1.6905]        8.7        7.4
Ahmed (2023)    3.2839 [ 2.4230; 4.1448]        1.8        6.3
Duran (2023)    0.2510 [-0.2950; 0.7970]        4.5        7.1
Elmahdy (2023)  2.0034 [ 1.6079; 2.3989]        8.5        7.4
Khalil (2024)   3.1841 [ 2.2219; 4.1462]        1.4        6.0

Number of studies combined: k = 14
Number of observations: o = 1529

                         SMD           95%-CI   z|t  p-value

Random effects model 1.1938 [0.6315; 1.7561]  4.59   0.0005

Quantifying heterogeneity:
 tau^2 = 0.8139 [0.4007; 2.5056]; tau = 0.9022 [0.6330; 1.5829]
 I^2 = 92.0% [88.3%; 94.5%]; H = 3.53 [2.92; 4.27]

Test of heterogeneity:
      Q d.f.  p-value
 161.99   13 < 0.0001

Details on meta-analytical method:
- Inverse variance method
- Restricted maximum-likelihood estimator for tau^2
- Q-Profile method for confidence interval of tau^2 and tau
- Hartung-Knapp (HK) adjustment for random effects model (df = 13)
- Cohen's d (standardised mean difference; using exact formulae)
```

Discussion

Over the past 2-3 decades, complications arising from diabetic retinopathy (DR) in type 2 diabetes mellitus (T2DM) have increased (Yau *et al*., 2012). Consequently, there is still a crucial need to identify biomarkers for the early prediction and diagnosis of DR. With this objective in mind, and supported by recent findings, a meta-analysis was carried out to explore the role of chemerin in T2DM patients, both with and without DR. This study evaluated the serum levels of circulating chemerin to determine their association with DR.

The study findings revealed that the pooled mean of serum chemerin in patients with DR was higher than without DR. Previous studieshad demonstrated that that chemerin significantly impacts DR development in many ways. By binding to its receptors, chemerin inhibits cAMP synthesis, activates hormone-sensitive lipase, boosts fat cell metabolism, and releases glycerol and FFAs. It also increases levels of human preadipocytes and 3T3-L1 cells during adipocyte differentiation,while shRNA inhibition of chemerin suppresses this process. Furthermore, chemerin promotes fat decomposition and enhances insulin sensitivity by increasing insulin-stimulated glucose transport (Liu *et al*., 2019). Chemerin found to control the key enzymes and adipokines, as well as the glucose transporter in mature adipocytes,which is involved in triglyceride synthesis (Luangsay *et al.,* 2009).

Overall, our study suggests that chemerin may contribute to the development of DR in patients with T2DM, likely through its involvement in inflammatory and angiogenic pathways and it could serve as a diagnostic biomarker for early detection and monitoring of DR.However, the study has a limitation as it does not involve healthy controls, which shall be addressed in future study.

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