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Malondialdehyde levels in diabetic retinopathy patients: a systematic review and meta-analysis

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Abstract

Background: It remains unclear whether circulating malondialdehyde (MDA) levels change in people with diabetic retinopathy (DR). This systematic review compared circulating MDA levels in diabetic people with and without DR.

Methods: PubMed, Medline (Ovid), Embase (Ovid), and Web of Science were searched for case-control studies conducted before May 2022 in English that compared circulating MDA levels in people with and without DR. The following MeSH search terms were used: ("malondialdehyde" or "thiobarbituric acid reactive substances [TBARS]" or "lipid peroxidation" or "oxidative stress") and "diabetic retinopathy." Newcastle–Ottawa Quality Assessment Scale was used to evaluate the quality of the included studies. Random-effects pairwise meta-analysis pooled the effect size with standardized mean difference (SMD) and 95% confidence intervals (CIs).

Results: This meta-analysis included 29 case-control studies with 1680 people with DR and 1799 people with diabetes but not DR. Compared to people without DR, the circulating MDA levels were higher in those with DR (SMD, 0.897; 95% CI, 0.631 to 1.162; $P < 0.001$). The study did not identify credible subgroup effects or publication bias and the sensitivity analysis confirmed the robustness of the study.

Conclusions: Circulating MDA levels are higher in people with DR compared to those without. Future comparative studies that use more specific methods are required to draw firm conclusions.

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Keywords: Malondialdehyde; Diabetic retinopathy; Lipid peroxidation; Oxidative stress

Introduction

Diabetic retinopathy (DR) is a progressive asymptomatic microvascular complication of diabetes that triggers irreversible retinal damage. It remains a major cause of sight-loss among the working-age populations of industrialized countries.[1] The prevalence of DR has continued to increase in many areas, such as East Asia, high-income America, Oceania, and southern Africa, while other diseases that cause blindness have decreased.[2] A global systematic review showed that there were approximately 103.12 million adults with DR worldwide in 2020, and the number would be 160.50 million by 2045.[3] As in China, we also are facing a challenge by the obesity pandemic.[4] Considering the close relationship between obesity and diabetes, it makes the research on diabetes and its complication such as DR in urgent need.

The pathophysiological mechanisms underlying the development of DR are still controversial. Currently, we believe that the expose of retina to hyperglycemia and other causal risk factors initiate a cascade of biochemical and physiological changes,[5] which finally bring about microvascular damage and retinal dysfunction.[6] There are several pathways of biochemical mechanisms modulating the pathogenesis of retinopathy: the accumulation of sorbitol and advanced glycation end-products, oxidative stress, protein kinase C activation, inflammation, and upregulation of the renin-angiotensin system and vascular endothelial growth factor, which are interrelated with each other.[7] Lipid peroxidation is one of the most important components of the response to oxidative stress.

Malondialdehyde (MDA) is one of the most widely used biomarkers for evaluating oxidative stress, as a secondary product of lipid peroxidation. Many animal trials have also supported the idea that higher circulating MDA levels could act as a predictor of DR.[8-10] Many studies have suggested that increased circulating MDA levels may be a risk factor in people with DR.[11-39] However, it is still unclear whether circulating MDA levels play a role in the

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evolution of DR. To clarify this relationship, we designed a meta-analysis to critically examine MDA levels in people with DR compared to people with diabetic mellitus (DM) but not DR.

Methods

Literature research strategies

We conducted this systematic review on MDA levels in people with DR according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses systematic review protocols. Several electronic databases were used, including PubMed, Medline (Ovid), Embase (Ovid), and Web of Science. The following MeSH search terms were used: ("malondialdehyde" or "thiobarbituric acid reactive substances [TBARS]" or "lipid peroxidation" or "oxidative stress") and "diabetic retinopathy." All English studies were conducted before May 2022, with no specified time span.

Criteria for inclusion and exclusion

The inclusion criteria for this study were as follows: (a) the study should be published in a journal in English; (b) the assessment of MDA levels (method description is provided for MDA estimation with mean and standard deviation [SD] values or any other data to calculate the mean and SD) should be feasible from the sample matrix, which should be available for both people with DR and DM subjects; (c) the study should be a case-control study design; and (d) we could obtain the full texts of the reported studies (not reviews, abstracts, posters, protocols, letters, comments, or editorial papers). The exclusion criteria were as follows: (a) they did not contain clear original data (efforts have been made to obtain data); (b) the subjects had a history of other diseases; (c) before MDA measurement, people received other treatments; (d) studies that do not provide information concerning clear clinical DR diagnoses.

Data extraction and management

We imported all obtained studies into an EndNote 20 library (EndNote^{TM} 20, Camelot UK Bidco Limited, Clarivate, UK) and removed duplicate studies. Two authors (JFW and ZL) independently screened eligible articles based on their abstracts and titles. If relevant, two investigators independently reviewed all the full articles. Furthermore, we manually reviewed all bibliographies of the published articles to define additional studies and identify one additional record. Both authors independently utilized standard extraction spreadsheets to extract data from the selected articles and listed them in a table. After the extraction, we cross-checked the data tables and discussed options to resolve conflicts and inconsistencies.

Quality assessment

We used the Newcastle–Ottawa Quality Assessment Scale (NOS) for case-control studies to evaluate the quality of the included studies. The NOS provides three main parts in nine points for each study: four for selection, two for comparability, and three for exposure. Two authors independently assessed all the included studies and discussed them to resolve discrepancies. NOS scores of 1 to 3 indicate low quality, 4 to 6 indicate moderate quality, and 7 to 9 indicate high quality.[40]

Statistical analysis

Statistical software named STATA 16 (Stata Corp, College Station, TX, USA) and Review Manager V5.4 (Cochrane Collaboration, Copenhagen, Denmark) were used for our meta-analysis. We calculated the standardized mean difference (SMD) with the corresponding 95% confidence interval (CI) for each parameter using the random-effects model (DerSimonian–Laird method) when I^2 was >50%. Statistical significance was set at $P < 0.05$. The overall effect size for SMD was presented using a Z-test (calculating each mean value and SD). We used I^2 to estimate the existence of heterogeneity and used chi-squared tests to examine the resultant P values. I^2 values of 25%, 50%, and 75% were defined as low, moderate, and high heterogeneity, respectively. Furthermore, forest plots adopted as the pooling method were used to evaluate the differences in MDA levels between people with DM but not DR and people with DR. If I^2 showed high heterogeneity, a subgroup analysis was performed to explore the source of heterogeneity. We also used a sensitivity analysis to assess robustness by omitting each study. To investigate publication bias, we visually evaluated the asymmetry of the funnel plot and used Egger's and Begg's biases. We used the trim-and-fill method to import potentially missing studies if publication bias was suspected.

Two authors (JFW and ZL) independently evaluated the quality of pooled evidence at the outcome level using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework. Any conflict was resolved by mutual consensus. Our study was conducted following the Meta-analysis of Observational Studies in Epidemiology guidelines. This study was registered in PROSPERO (https://www.crd.york.ac.uk/PROSPERO/; No. CRD42022352640).

Results

Literature research and study characteristics

As shown in Figure 1, we searched four databases and found 7357 records, and also identified 1 record from searching citation. After reviewing the titles and abstracts, 7276 were excluded because they were duplicates, unrelated, reviews, animal studies, or meeting abstracts. Subsequently, 49 articles were excluded after reading their full text. In total, 29 case-control studies were enrolled in our meta-analysis.[11-39] A total of 1680 people with DR and 1799 people with diabetes but not DR were included in our meta-analysis. The basic characteristics and NOS scores of the studies are presented in Table 1.

Overall and subgroup analysis

The forest plot for MDA concentrations in people with DR and diabetic mellitus without diabetic retinopathy

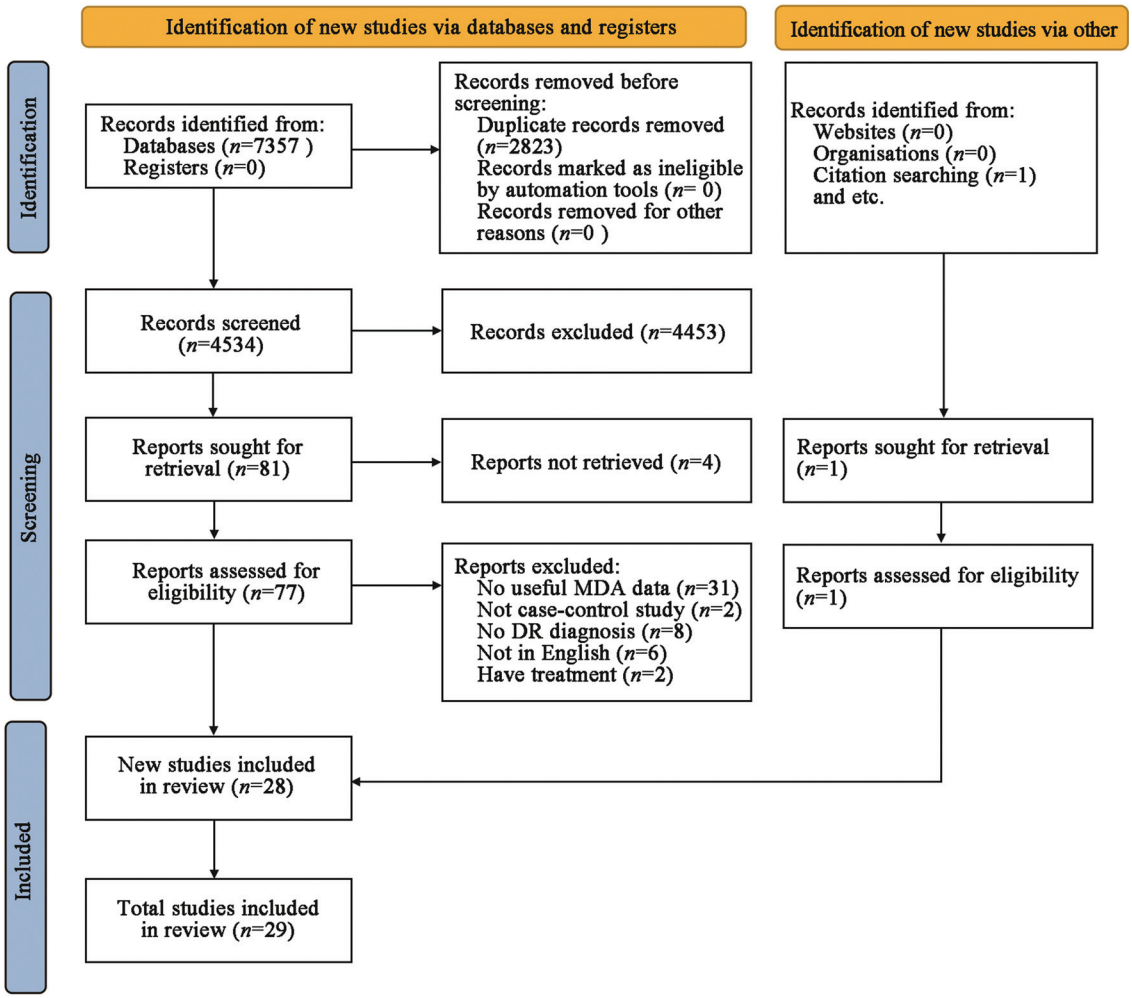

Figure 1: Flowchart for study selection. DR: Diabetic retinopathy; MDA: Malondialdehyde.

(NDR) from the random-effects meta-analysis that combined SMD is presented in Figure 2. MDA levels were significantly higher in the DR group than in the NDR group (SMD, 0.897; 95% CI, 0.631–1.162), but we observed an obvious heterogeneity among the 29 studies ($I^2 = 92.03\%$). Subgroup and meta-regression analyses were performed to analyze the source of heterogeneity. Subgroup analysis was conducted by year of publication, sex, age, duration of DM, study size, NOS score, continent, MDA assay type, MDA sample matrix, MDA absorption, and DR type. The results of almost all subgroups showed that MDA levels in the DR group were significantly higher than those in the NDR group [Table 2]. Meta-regression results indicated that the type of MDA assay and MDA absorption spectrum might slightly contribute to the heterogeneity ($R^2 = 7.50\%$ and $R^2 = 14.82\%$, respectively).

Sensitivity analysis

To assess the stability and reliability of our results, we performed a sensitivity analysis. SMD was not affected by the removal of each study from the pooled analysis [Table 3].

Publication bias

From the Begg and Egger tests, we found no publication bias in our study ($P = 0.568$ and $P = 1.000$, respectively). Visual examination of the funnel plot revealed publication bias on the right side. Therefore, trim-and-fill analysis was performed, and it was confirmed that the contour-enhanced funnel plot after trim-and-fill showed that all inputted studies were located in the statistically significant area, which indicated that visual asymmetry would have some extra reasons in addition to publication bias.

GRADE quality of evidence

Using the GRADE framework, we judged the overall quality of evidence for our outcome to be moderate.

Discussion

This meta-analysis assessed the association of MDA levels with DR. The results showed that circulating MDA levels were significantly higher in people with DR than in people with DM but not DR. Observing the extreme heterogeneity in our study, we should explain the results with prudence.

Table 1: Characteristics of the included studies.

							DM without DR					DR					
Study	Country	Sample Matrix	Assay Type	NOS score/9	Continent	MDA unit	*n*	Mean Age	Sex (Male/Female)	MDA levels Mean ± SD	DM type	*n*	Mean Age	Sex (Male / Female)	MDA levels Mean ± SD	DR type	Significant results of MDA levels
Dave *et al*[11]	India	Serum	Colorimetric	7	Asia	nmol/mL	44	52.05	46/34 (N DR + DR)	3.655 ± 2.278	T2DM	4PDR 32NPDR	PDR: 57.00 NPDR: 56.13	NR	PDR: 3.820 ± 1.965; NPDR: 2.919 ± 1.142	PDR and NPDR	It was not different in patients with and without DR, and thus it cannot be used as a marker for prediction of development of DR.
Mondal *et al*[12]	India	Serum	Colorimetric	9	Asia	nmol/mL	100	NR	55/45	2.61 ± 1.10	T2DM	42	NR	NR	3.95 ± 1.40	PDR	In this study, the estimation of MDA demonstrated significantly higher levels in PDR participants as compared to diabetics with no retinopathy.
Sanz-González *et al*[13]	Spain	Plasma	Spectrophoto metry	8	Europe	μmol/L	52	65.0	46%/54%	3.0 ± 0.2	T2DM	69	NR	NR	3.7 ± 0.2	NPDR	Furthermore, significantly higher plasma levels of MDA/TBARS were observed in the T2DM + DR with respect to the NDR patients.
Verma *et al*[14]	India	Serum	Colorimetric	5	Asia	μmol/L	54	NR	NR	2.12 ± 1.55	T2DM	54	NR	NR	4.25 ± 1.03	NR	MDA was highly significantly ($P = 0.0001$) higher among cases (4.25 ± 1.03) than controls (2.12 ± 1.55).
Fahmy *et al*[15]	Saudi Arabia	Serum	Spectrophoto metry	9	Asia	μmol/mL	12	52.41	NR	0.08 ± 0.0320	T2DM	12	46.83	NR	0.08 ± 0.0157	NR	GST and lipid peroxides did not show any significant difference between the three studied groups.
Dai *et al*[16]	China	Serum	Colorimetric	9	Asia	μmol/L	52	53.21	29/23	11.48 ± 3.19	T2DM	52	52.64	27/25	17.80 ± 4.34	PDR	The MDA levels in the NDR group were significantly lower than the DR group, with statistical significance ($P < 0.05$).
Kuppan *et al*[18]	India	Plasma	Spectrophoto metry	7	Asia	μmol/L	22	51	14/8	72.37 ± 44.15	T2DM	22PDR 21NPDR	PDR: 52 NPDR: 58	PDR: 19/3; NPDR: 15/6	PDR: 115.34 ± 114.18; NPDR: 98.79 ± 53.99	PDR and NPDR	There was a significant increase in the levels of plasma MDA in the DR cases compared to that of control.
Roig-Revert *et al*[19]	Spain	Plasma	Spectrophoto metry	8	Europe	μm/L	68	62.3	51.4%/48.6%	2.37 ± 1.39	T2DM	62	65.1	47.3%/52.7%	3.63 ± 1.30	NR	The MDA/TBARS displayed significantly higher in the T2DMG + DR with respect to those diabetics without DR and the CG.
Shawki *et al*[20]	Egypt	Serum	Colorimetric	7	Africa	μmol/L	40	45.4	14/26	12.00 ± 4.99	NR	70	43.0	30/40	18.60 ± 3.67	NR	The levels of serum MDA were significantly higher in type 2 diabetics than healthy controls.
Choudhuri *et al*[21]	India	Serum	ELISA	8	Asia	Pmol/mL	100	49.4	54/46	118.3 ± 35.6	T2DM	100	51.8	56/44	134.7 ± 36.3	NPDR	Further, subjects with NPDR showed higher levels of serum MDA protein adduct than the NDR group, and the difference was statistically significant ($P = 0.0009$).
Vivian Samuel *et al*[22]	India	Serum	Spectrophoto metry	6	Asia	μmol/L	30	50.6	NR	4.63 ± 0.58	T2DM	30	49.5	NR	6.72 ± 0.20	DR and DME	The levels of serum MDA levels were significantly higher compared with those of the control group ($P < 0.001$). The levels of serum MDA of the group with retinopathy were significantly higher ($P < 0.001$) than the group without retinopathy.
Aldebasi *et al*[17]	Saudi Arabia.	Plasma	spectrophoto metry	8	Asia	μmol/L	33	51.82	14/19	2.79 ± 0.5745	T2DM	21	60.38	8/13	3.43 ± 0.4583	PDR	Moreover, the lipid peroxidation marker, MDA, was significantly higher (P = 0) in diabetics with proliferative retinopathy than in subjects in control groups. Data showed that, when compared to diabetics without retinopathy, patients with PDR were characterized by significantly higher MDA (P = 0).
Kurtul *et al*[23]	Turkey	Leuk ocytes	Spectrophoto metry	5	Asia	nmol/mg protein	16	59.00	NR	3.95 ± 0.98	T2DM	PDR: 10; BDR (NPDR):	PDR 57.00 BDR (NPDR):	NR	PDR: 5.54 ± 1.72; BDR (NPDR):		MDA concentrations rose with increasing severity of DR.

(*continued*)

Table 1
(continued).

Study	Country	Sample Matrix	Assay Type	NOS score/9	Continent	MDA unit	DM without DR					DR					Significant results of MDA levels
							n	Mean Age	Sex (Male/Female)	MDA levels Mean ± SD	DM type	*n*	Mean Age	Sex (Male / Female)	MDA levels Mean ± SD	DR type	
												7; prePDR 8; T2DR: 25	55.85; prePDR: 54.25; T2DR: 55.80		4.19 ± 1.11; prePDR: 4.30 ± 0.76; T2DR: 4.76 ± 1.42	BDR (NPDR); prePDR; PDR; T2DR	However, MDA levels and SOD and CAT activities were not different in type 2 diabetic patients with retinopathy compared to those without retinopathy.
Gupta *et al*[24]	India	Blood samples	Condense with 1 methyl 2 phenyl indole	8	Asia	μmol/L	40	50	27/13	1.72 ± 0.27	NR	PDR: 22; NPDR: 20	PDR: 46; NPDR: 47	PDR: 10/ 12; NPDR: 9/ 11	PDR: 1.93 ± 0.25; NPDR: 1.98 ± 0.20	PDR and NPDR	The levels of MDA ($P < 0.001$ and $P < 0.05$) were significantly increased in diabetics with proliferative retinopathy when compared with the controls and the diabetic group without complications. The levels of MDA ($P < 0.001$ and $P < 0.01$) were significantly increased in diabetics with non-proliferative retinopathy when compared with the control and the diabetic group without complications.
Losada and Alio[25]	Spain	Plasma	Spectrophotometry	6	Europe	mmol/L	28	26.92	12/16	1.80 ± 0.81	T1DM	32	38.81	17/25	2.65 ± 1.00	NR	We have found that the diabetics with retinopathy show MDA levels that are significantly higher than in the control group and in the diabetics without retinopathy ($P < 0.001$). We have not found any significant statistical differences among the other groups ($P > 0.05$).
Sharma *et al*[26]	India	Plasma	Spectrophotometry	7	Asia	μmol/L	20	52.4	12/8	2.56 ± 4.1452	T2DM	PDR: 20 NPDR: 20	PDR: 53.5 NPDR: 56.2	PDR: 13/ 7 NPDR: 13/7	PDR: 3.01 ± 2.8632 NPDR: 3.1100 ± 3.8674	PDR and NPDR	Analysis revealed that increased levels of plasma LPO were associated with increased severity of DR.
Kundu *et al*[27]	India	Plasma	Spectrophotometry	9	Asia	μmol/L	50	56.20	39/11	6.44 ± 1.53	T2DM	50	58.56	36/14	6.65 ± 0.30	NR	We found increased lipid peroxidation in terms of MDA in diabetics compared with controls and this increase was larger in DR.
Vidya *et al*[28]	India	Plasma	Spectrophotometry	6	Asia	nmol/dL	25	48.6	NR	473.01 ± 111.65	T2DM	50	53.6	NR	1041.90 ± 664.20	NR	The levels of MDA were significantly higher in the diabetics without retinopathy as compared to those of the control group ($P < 0.001$). The levels of MDA were significantly higher in the diabetics with retinopathy, as compared to those in the diabetes without retinopathy group ($P < 0.001$).
Khalili *et al*[29]	Iran	Plasma	Spectrophotometry	8	Asia	μmol/L	100	55.9	28/72	6.6 ± 1.9	T2DM	100	58.5	35/65	6.7 ± 2.0	NR	A significantly higher level of MDA (6.7 ± 2.0 nmol/mL) was observed in patients with retinopathy compared to the control group.
Mandal *et al*[30]	India	Serum and vitreous	Spectrophotometry	8	Aisa	nmol/L	32	49.5	22/10	Serum: 3.10 ± 1.83 Vitreous: 1.21 ± 0.32	T2DM	45	51.7	26/19	Serum: 4.65 ± 1.79 Vitreous: 1.65 ± 0.67	PDR	A noticeable increase in serum and vitreous MDA level was observed among PDR subjects compared with NDR ($P = 0.0004$ and $P = 0.0058$, respectively) and HC individuals ($P < 0.0001$ and $P = 0.0003$, respectively). Yet again, the serum MDA level was significantly low in healthy individuals even compared with NDR subjects ($P = 0.027$).
Gaonkar *et al*[31]	India	Plasma	Colorimetry	8	Asia	μmol/L	148	59.3	NR	0.55 ± 0.08	T2DM	PDR: 74 NPDR: 148	PDR: 62.0 NPDR: 58.6	NR		PDR and NPDR	A significantly higher plasma MDA concentration was

(*continued*)

Table 1

(continued).

Study	Country	Sample Matrix	Assay Type	NOS score/9	Continent	MDA unit	DM without DR					DR					Significant results of MDA levels
							n	Mean Age	Sex (Male/Female)	MDA levels Mean ± SD	DM type	*n*	Mean Age	Sex (Male / Female)	MDA levels Mean ± SD	DR type	
															PDR: 0.71 ± 0.12 NPDR: 0.60 ± 0.12		observed in NPDR and PDR groups.
Kumari *et al*[32]	India	Plasma	Spectrophoto metry	8	Asia	μmol/L	36	55.30	NR	1.67 ± 0.14	T2DM	50	63.04	NR	2.02 ± 0.14	NR	Lipid peroxidation marker MDA was significantly elevated ($P < 0.001$) in both the diabetic groups as compared to controls.
Turk *et al*[33]	Turkey	Serum	Spectrophoto metry	7	Asia	μmol/L	35	55.74	13/22	0.325 ± 1.4268	T2DM	35	60.00	15/20	0.244 ± 1.3032	NR	The MDA levels of patients with DR were lower than those without DR. In ROC analysis conducted for MDA levels, we observed that MDA did not reflect DR at a sufficient level of specificity and sensitivity.
Longo-Mbenza *et al*[34]	South Africa	Serum	HPLC	8	Africa	mmol/L	84	56.6	39/45	9.1 ± 5.2	T2DM	66	53.4	26/40	8.7 ± 2.5	NR	The highest levels of TBARS among the present T2DM group with DR confirmed the significant impact of the imbalance of oxidant/ antioxidant status in the pathophysiology of DR from several studies.
Gürler *et al*[35]	Turkey	Serum	Spectrophoto metry	9	Asia	μmol/L	34	51.79	21/13	3.38 ± 0.95	NR	25	54.60	17/8	4.38 ± 1.31	NR	LPO assessment of the groups suggested that all subjects with DM showed an increased LPO, and there were statistically significant differences between the DR and NDR groups.
El-Mesallamy *et al*[36]	Egypt	Serum	Spectrophoto metry	6	Africa	μmol/L	23	54.65/57.92	11/12	5.28 ± 1.6306	T2DM	PDR: 22 NPDR: 22	PDR: 59.65/5 9.13 NPDR: 54.11/58.82	PDR: 14/ 8 NPDR: 9/ 11	PDR: 6.81 ± 2.2983 NPDR: 5.57 ± 2.0169	PDR and NPDR	MDA levels in PDR are significantly different from the type II DM group at $P \leq 0.03$, and PDR is significantly different from the NPDR group at $P \leq 0.03$.
Hartnett *et al*[37]	USA	Serum	HPLC	9	America	mmol/L	18	NR	NR	2.76 ± 0.89	T1DM and T2DM	Advance d risk: 23; Moderat e risk: 31	NR	NR	Advanced risk: 2.86 ± 1.45; Moderate risk: 2.33 ± 1.19	(1) low risk (no retinopathy), (2) moderate risk (mild and moderate NPDR), or (3) advanced risk (severe NPDR, very severe NPDR, and all PDR).	We found that levels of TBARS were significantly elevated in patients with diabetes compared with those in control subjects, which supports the findings by others. We were unable to support the hypothesis of an association between severity of DR and TBARS as a measure of oxidative stress.
Icel *et al*[38]	Turkey	Serum	Spectrophoto metry	7	Asia	μmol/L	39	57.56	12/27	2.53 ± 1.13	T2DM	PDR: 55 NPDR: 42	PDR: 60.00 NPDR: 59.50	PDR: 22/ 33 NPDR: 20/22	PDR: 5.79 ± 1.16; NPDR: 2.74 ± 1.63	PDR and NPDR	There is a significant increase in MDA levels with an advance in DR.
Kumari *et al*[39]	India	Plasma	Spectrophoto metry	8	Asia	μmol/L	30	56.30	NR	1.69 ± 0.15	T2DM	42	64.07	NR	2.02 ± 0.14	NR	MDA registered a higher value in DR than the control group.

TBARS: Thiobarbituric acid reactive substances; T1DM: Type 1 diabetic mellitus; T2DM: Type 2 diabetic mellitus; MDA: Malondialdehyde; NDR: Diabetic mellitus without diabetic retinopathy; PDR: Proliferative diabetic retinopathy; NPDR: Non-proliferative diabetic retinopathy; CG: Control group; HC: Healthy control; ELISA: Enzyme-linked immunosorbent assay; HPLC: High performance liquid chromatography; GST: Glutathione S-transferase; DME: Diabetic macular edema; BDR: Background diabetic retinopathy; prePDR: Preproliferative diabetic retinopathy; T2DR: Type 2 diabetic retinopathy; SOD: Superoxide dismutase; CAT: Catalase; LPO: Lipid peroxidation; ROC: Receiver operating characteristic; NR: Not reported; DR: Diabetic retinopathy; DM: Diabetic mellitus; NOS: Newcastle–Ottawa Quality Assessment Scale; SD: Standard deviation.

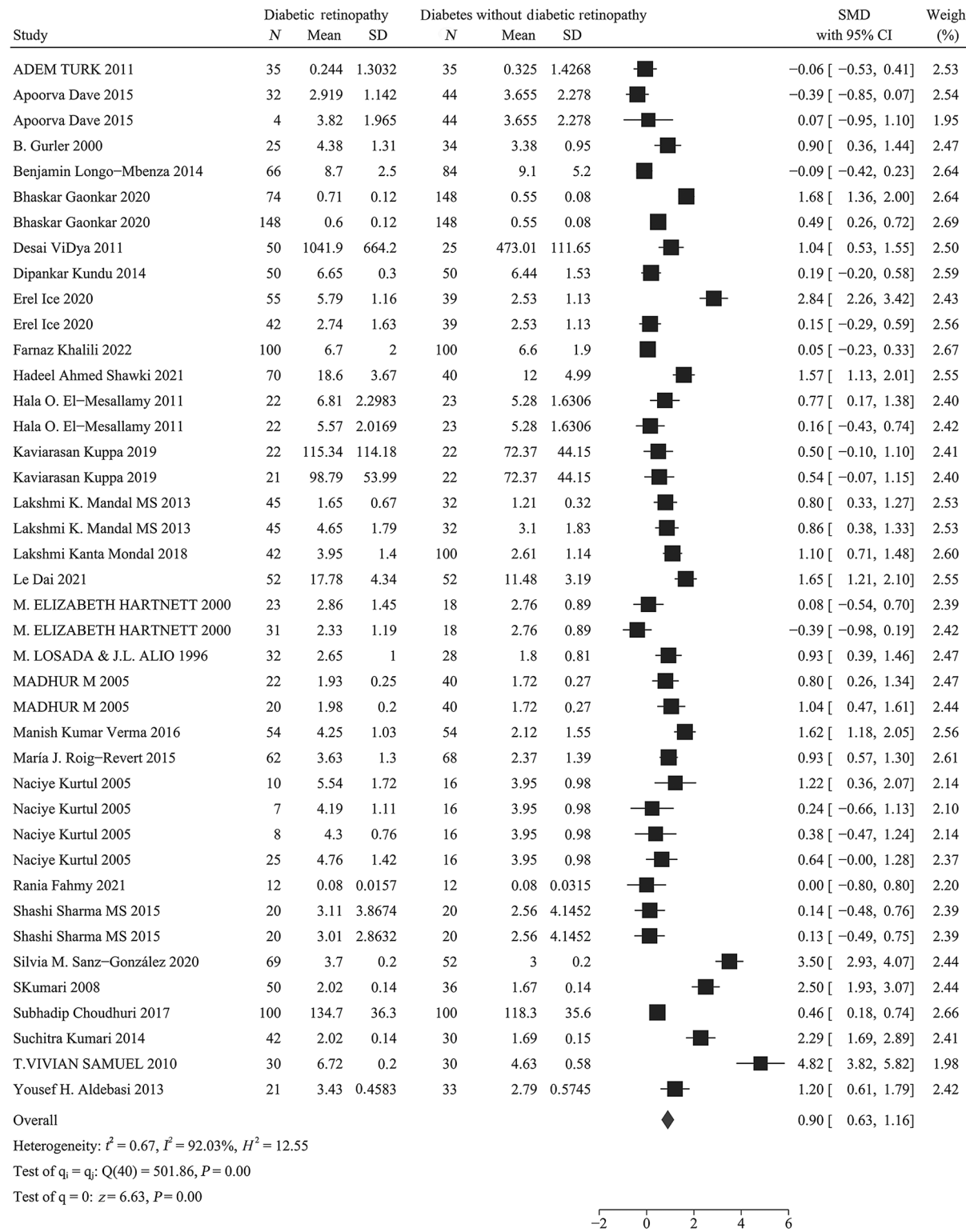

Figure 2: Forest plot of studies examining MDA level and DR. CI: Confidence interval; DR: Diabetic retinopathy; MDA: Malondialdehyde; SMD: Standardized mean difference.

The complexity and diversity of mechanisms make it important to identify more biomarkers to stratify the risk of DR. MDA, as a popular biomarker of oxidative stress with many available measurement methods, was chosen to be a potential predictor of DR.

When oxidative stress is not controlled, the hydroxyl radical oxidizes lipids that contain carbon–carbon double bonds, particularly polyunsaturated fatty acids (PUFAs)[41] and produces various bioactive aldehydes with toxicity. The secondary products of lipid peroxidation, MDA,

Table 2: Subgroup meta-analysis and meta-regression on the relationship between MDA levels and risk of DR.

Subgroups	MDA levels in DR and NDR					
	No. of study*	SMD (95% CI)	I^2 (%)	*P* for heterogeneity	*P* for Meta-regression	*P* for Group differences
Overall	29	0.897 (0.631, 1.162)	92.03	<0.001‡		
Year of publication					0.414	0.511
≤2010	7	1.066 (0.450, 1.682)	90.82	<0.001‡		
>2010	22	0.836 (0.537, 1.136)	92.59	<0.001‡		
Gender†					0.668	0.696
Male/Female≥1	10	0.814 (0.267,1.360)	94.24	<0.001‡		
Male/Female<1	13	0.693 (0.431, 0.955)	81.23	<0.001‡		
Age (years)					0.847	0.816
≥55	12	0.857 (0.467, 1.247)	92.77	<0.001‡		
<55	15	0.925 (0.503, 1.348)	92.10	<0.001‡		
Duration of diabetes mellitus					0.239	0.905
>10	13	0.819 (0.393, 1.245)	87.66	<0.001‡		
≤10	9	0.853 (0.493, 1.213)	92.97	<0.001‡		
Study size (total number)					0.999	<0.001‡
(51,100]	16	0.810 (0.415, 1.204)	90.86	<0.001‡		
(101,150]	8	1.385 (0.936, 1.834)	89.98	<0.001‡		
(151,200]	3	0.144 (−0.179, 0.466)	72.44	0.027‡		
NOS score					0.602	0.267
5	2	0.872 (0.287, 1.457)	71.06	0.008‡		
6	4	1.474 (0.378, 2.570)	93.80	<0.001‡		
7	6	0.555 (−0.056, 1.165)	91.92	<0.001‡		
8	11	1.154 (0.703, 1.606)	94.73	<0.001‡		
9	6	0.530 (−0.016,1.162)	87.71	<0.001‡		
Continent					0.698	0.424§
Asia	22	0.948 (0.643, 1.253)	92.25	<0.001‡		
Africa	3	1.439 (0.496, 2.382)	91.25	<0.001‡		
America	1	−0.167 (−0.632, 0.298)	NA	NA		
Europe	3	0.599 (−0.234, 1.432)	92.08	<0.001‡		
MDA sample matrix					0.440	0.439
Serum	15	0.820 (0.396, 1.245)	93.13	<0.001‡		
Plasma	12	1.065 (0.611, 1.520)	93.93	<0.001‡		
Types of DR					0.590	0.593
PDR	12	0.989 (0.494, 1.485)	91.26	<0.001‡		
NPDR	12	0.803 (0.336, 1.270)	92.22	<0.001‡		
MDA assay type					0.054	0.998‖
Spectrophotometry	19	1.004 (0.629, 1.378)	92.03	<0.001‡		
Colorimetric	6	1.009 (0.484, 1.533)	92.80	<0.001‡		
HPLC	2	−0.122 (−0.379,0.135)	0	0.530		
1-methyl-2-phenyl-indole	1	0.914 (0.523, 1.305)	NA	NA		
ELISA	1	0.456 (0.175, 0.737)	NA	NA		
MDA absorption spectrum					0.057	<0.001¶
400nm	2	−0.122 (−0.379, 0.135)	0	0.530		
530nm	2	1.710 (0.082, 3.338)	96.83	<0.001‡		
532nm	5	0.516 (0.183, 0.850)	57.64	0.015‡		
535nm	6	1.186 (0.360, 2.012)	93.35	<0.001‡		

* As some of the articles did not clearly indicate the relevant information, only articles with clear relevant information were included in the subgroup analysis. † Male/Female≥1: The ratio of the number of males to the number of females is greater than or equal to 1; Male/Female<1: The ratio of the number of males to the number of females is less than 1. ‡ Significant differences. § Only compared group African, group Asian, and group European for a sufficient number of studies. ‖ Only compared group spectrophotometry and group colorimetric for a sufficient number of studies. ¶ Only compared group 532 nm and group 535 nm for a sufficient number of studies. MDA: Malondialdehyde; CI: Confidence interval; DR: Diabetic retinopathy; NDR: Diabetic mellitus without diabetic retinopathy; ELISA: Enzyme-linked immunosorbent assay; HPLC: High performance liquid chromatography; ELISA: Enzyme linked immunosorbent assay; SMD: Standard mean difference; PDR: Proliferative diabetic retinopathy; NPDR: Non-proliferative diabetic retinopathy; NA: Not available; NOS: Newcastle–Ottawa Quality Assessment Scale.

Table 3: Sensitivity analysis.

Study	SMD	95% CI	
		Lower CI limit	Higher CI limit
Turk *et al*[33]	0.921	0.653	1.189
Dave *et al*[11]	0.929	0.664	1.194
Dave *et al*[11]	0.912	0.645	1.180
Gürler *et al*[35]	0.896	0.626	1.167
Longo-Mbenza *et al*[34]	0.923	0.656	1.190
Gaonkar *et al*[31]	0.874	0.608	1.140
Gaonkar *et al*[31]	0.908	0.629	1.187
Vidya *et al*[28]	0.892	0.622	1.163
Kundu *et al*[27]	0.915	0.644	1.185
Icel *et al*[38]	0.916	0.646	1.185
Icel *et al*[38]	0.846	0.590	1.103
Khalili *et al*[29]	0.919	0.649	1.188
Shawki *et al*[20]	0.878	0.610	1.146
El-Mesallamy *et al*[36]	0.914	0.645	1.183
El-Mesallamy *et al*[36]	0.899	0.629	1.169
Kuppan *et al*[18]	0.906	0.636	1.176
Kuppan *et al*[18]	0.905	0.635	1.175
Mandal *et al*[30]	0.899	0.627	1.170
Mandal *et al*[30]	0.897	0.626	1.168
Mondal *et al*[12]	0.891	0.619	1.163
Dai *et al*[16]	0.876	0.608	1.144
Hartnett *et al*[37]	0.916	0.647	1.184
Hartnett *et al*[37]	0.928	0.662	1.194
Losada and Alio[25]	0.895	0.625	1.166
Madhur [24]	0.899	0.628	1.169
Madhur[24]	0.892	0.622	1.162
Verma *et al*[14]	0.877	0.609	1.145
Roig-Revert *et al*[19]	0.895	0.622	1.169
Kurtul *et al*[23]	0.889	0.621	1.157
Kurtul *et al*[23]	0.902	0.633	1.172
Kurtul *et al*[23]	0.907	0.639	1.176
Kurtul *et al*[23]	0.910	0.642	1.178
Fahmy *et al*[15]	0.916	0.648	1.184
Sharma *et al*[26]	0.914	0.646	1.183
Sharma *et al*[26]	0.915	0.646	1.184
Sanz-González *et al*[13]	0.829	0.583	1.074
Kumari *et al*[32]	0.855	0.594	1.116
Choudhuri *et al*[21]	0.909	0.633	1.184
Kumari *et al*[39]	0.861	0.598	1.125
Vivian Samuel *et al*[22]	0.818	0.566	1.069
Aldebasi *et al*[17]	0.888	0.619	1.158
Overall	0.896	0.631	1.160

CI: Confidence interval; SMD: Standardized mean difference.

4-Hydroxynonenal (4-HNE), and acrolein, can adduct with cellular proteins, and protein carbonylation participates in the development of diabetes by activating the other pathways or factors and causes harm to the structure and function of the retina.[42] The uncontrolled oxidative stress would account for the increased MDA levels in people with DR compared to people with DM but not DR.

We have found evidence that circulating MDA might have some combination with sex, age, and diabetes duration.[43-45] However, in our subgroup analysis of sex, age, and duration of DM, we found no significant differences among subgroups. We supposed that it is the limit on the number of studies that resulted in us being able to collect only the data of the mean of ages, the proportion of sex, and the mean of diabetes duration of each study. More specific data and more meticulous divided subgroups might lead to more reliable results.

In the field of statistics, we considered that the publication year, the study location, and the study size might affect our results, but we only found significant differences between subgroups in analyzing the number of people included in the studies (study size). Furthermore, heterogeneity slightly decreased when divided into different groups by study size (changed to 90.86%, 89.98%, and 72.44%). We also compared different studies on NOS scores to evaluate whether the quality of the studies is relevant. In addition, there were no significant differences between the groups. These results suggest that statistical differences between our involved studies have slight effects on the extreme heterogeneity mainly because of study size.

Based on the absence or presence of neovascularization, people with DR are classified as having non-proliferative diabetic retinopathy (NPDR) or proliferative diabetic retinopathy (PDR).[46] Therefore, in the study design, we suspected that MDA levels in NPDR should be lower than those in PDR. Surprisingly, we did not observe a significant difference between the NPDR and PDR groups. At the same time, meta-regression did not find a relationship between DR type and high heterogeneity. This finding might show that lipid peroxidation has limited effect on neovascularization compared with other mechanisms, and thus the differences of MDA levels between NPDR and PDR could not be found in our study.

In meta-analysis, SMD is used as a summary statistic when all the studies evaluate the same outcome, but they do that in different ways. However, the different approaches of MDA measurement may lead to different results. We found that the subgroup of the TBARS assay with different absorption spectra showed statistically significant differences, and in the meta-regression, both the MDA assay type and absorption spectrum contributed to high heterogeneity. Some studies have also reported that TBARS assays lack specificity because thiobarbituric acid can react with other compounds,[47,48] and the difference in total MDA in human plasma was up to three-fold when measured by TBARS compared to that by high performance liquid chromatography (HPLC) in human plasma.[49] However, we found only two studies using HPLC in our included studies.[34,37] The most widely used method in our meta-analysis is TBARS. In general, the high heterogeneity of our study might have been caused by different MDA assays and non-specific TBARS methods.

Our study had several strengths and limitations. The current meta-analysis of case-control studies evaluated the circulating MDA levels in people with DR *vs.* people with DM but not DR. The sensitivity analysis revealed that none of the studies individually influenced the overall SMD, indicating that after removing any single study, an increase in the MDA levels of DR people was still evident. We also predesigned a couple of subgroup analyses to

assess the role of MDA in DR in various aspects. Then, the high heterogeneity might be attributable to various environmental factors, diet and lifestyle habits, TBARS methods, and methodological limitations of case-control study design. We suspect that the TBARS method has a low specificity, which could be a major source of heterogeneity. But our included studies are all cross-sectional studies with a case control designed. This type of design usually cannot establish the temporal relationship between exposure and disease; thus, the causation and its underlying mechanisms between MDA and DR can be unclear. To ascertain the cause–effect correlation, more prospective studies are needed, especially prospective cohort studies.

In summary, this study supports that the view that circulating MDA levels increased in people with DR compared to those with DM but not DR. However, the presence of marked heterogeneity makes this finding debatable. Further high-quality epidemiologic studies in cohort design with more specific methods are necessary to determine the concrete mechanisms and effects of MDA. At this stage, no recommendation can be made regarding routine investigation and treatment of elevated MDA in DR.

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Conflicts of interest

None.

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