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Association between the soluble receptor for advanced glycation end products and diabetes mellitus: systematic review and meta-analysis

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Abstract

Background and Aims In both type 1 diabetes (T1DM) and type 2 diabetes (T2DM), previous studies have yielded inconsistent findings regarding whether the levels of the soluble receptor for advanced glycation end products (sRAGE) are significantly altered. This meta-analysis aims to systematically evaluate the changes of sRAGE levels in patients with T1DM and T2DM.

Methods PubMed, Embase, and Web of Science were systematically searched from inception until April 2024. We included studies reporting sRAGE levels in individuals with T1DM or T2DM, using non-diabetic healthy individuals as the control group. A random-effects model was applied to conduct a meta-analysis of effect measures (means and SDs).

Results 49 datasets from 32 studies, involving 4948 subjects, met the inclusion criteria. A random-effects model meta-analysis showed that sRAGE levels in T1DM subjects (SMD 0.45, CI: 0.16–0.73, $P=0.002$) and T2DM subjects with complications (SMD 1.59, CI: 0.77–2.41, $P=0.0001$) were significantly higher than those in the control groups. No statistically significant change in sRAGE levels was observed in T2DM subjects without complications (SMD 0.01, CI: -0.61–0.64, $P=0.97$). A decrease in sRAGE levels was observed in subjects with newly diagnosed T2DM (SMD-0.40, CI: -0.71– -0.09, $P=0.01$).

Conclusion This meta-analysis indicated that sRAGE levels increased in T1DM patients and T2DM patients with complications, while they decreased in newly diagnosed T2DM patients. No significant difference was observed in T2DM patients without complications. Clearly, changes in sRAGE levels in patients with T1DM or T2DM are not uniform, but depend on the different types and stages of the disease.

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Keywords Soluble receptor for advanced glycation end products, sRAGE, Type 1 diabetes, Type 2 diabetes

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Introduction

Chronic complications of diabetes are a major cause of disability and mortality in diabetic populations, significantly increasing the public health expenditures related to diabetes. One of the major mechanisms underlying the development and progression of these complications involves advanced glycation end products (AGEs) and their associated molecular pathways [1].

Advanced glycation end products (AGEs) are a group of heterogeneous molecules produced through the non-enzymatic glycation and oxidation of proteins, lipids, and nucleic acids [1]. AGEs formation proceeds slowly under euglycemic conditions, but is accelerated in hyperglycemia, oxidative stress, and situations where protein and lipid turnover is prolonged [1]. AGEs can directly capture and crosslink proteins, or activate signaling pathways by binding to advanced glycation end product receptors (RAGE), also known as full-length RAGE (fl-RAGE) on the cell surface, leading to impaired pancreatic β-cell function and peripheral tissue insulin resistance [2].

In addition to AGEs, RAGE can bind to other ligands, including high-mobility group box protein 1 (HMGB1), S100 proteins, β-amyloid, β-sheet fibrils, and lipopolysaccharides [1]、 [3]. Physiologically, RAGE expression is typically low in tissues. However, in metabolic, inflammatory, and age-related diseases, elevated RAGE expression is commonly observed [4]. Besides being located on the cell membrane, RAGE also exists in soluble forms, including endogenous secretory RAGE (esRAGE) and cleaved RAGE (cRAGE). esRAGE is a splice variant of RAGE secreted by cells, while cRAGE is proteolytically cleaved from fl-RAGE by matrix metalloproteinases (MMPs) [1]. They are collectively referred to as soluble receptors for advanced glycation end products (sRAGE). sRAGE circulates in the bloodstream and competes with fl-RAGE, reducing ligand availability by binding to or sequestering RAGE ligands [3]. Therefore, sRAGE is recognized as a protective receptor.

Numerous studies have reported that elevated sRAGE levels in patients with diabetes are closely related to cardiovascular complications [5], renal complications [6], and even mortality [5]、 [6]. The changes of sRAGE levels in diabetes patients compared with non-diabetic healthy individuals can predict the complications, suggesting that sRAGE can be used as a predictor of diabetes complications. However, in either type 1 diabetes (T1DM) or type 2 diabetes (T2DM), previous studies [7–38] have been inconsistent regarding whether sRAGE levels are significantly altered. Some studies [7, 8, 10, 13–20, 22, 23, 28, 30, 31, 33] have confirmed that sRAGE levels in patients with diabetes are higher those in healthy individuals, while others [9, 11, 21, 27, 32, 34, 36–38] have shown that they are lower. Additionally, some studies others [12, 13, 17, 24–26, 29, 31, 35] have indicated no difference between the two groups. These inconsistent conclusions have caused confusion among researchers. Currently, no comprehensive analysis has been conducted on the relationship between sRAGE and diabetes. In this context, we performed a meta-analysis to investigate sRAGE levels in patients with diabetes, thereby providing substantial insight into the relationship between sRAGE and diabetes.

Research design and methods

This meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), and was registered in PROSPERO under registration number CRD42024521252.

Search strategy

We searched the PubMed, Embase, and Web of Science databases from inception to April 2024. Medical Subject Headings (MeSH) such as 'Receptor for Advanced Glycation End Products,' 'Diabetes Mellitus,' 'Diabetes Mellitus, Type 1,' 'Diabetes Mellitus, Type 2,' and related text words were used to identify studies evaluating circulating sRAGE concentrations in patients with type 1 or type 2 diabetes. The details of the search strategy are provided in the Supplementary Material.

Study selection

Relevant studies were independently selected by three investigators (Q. C., W.K., and X.L.). Any conflicts were resolved by consensus or through consultation with a fourth investigator (Y.L.). We defined the inclusion criteria based on a specific population (P), intervention (I), comparator (C), and outcome (O), as recommended by PRISMA. We included studies that reported serum concentrations of sRAGE (O) in patients with type 1 or type 2 diabetes (P). The control groups were non-diabetic healthy individuals (C). No study type restrictions were applied. We excluded studies with incomplete data, studies involving diabetic patients with severe comorbidities (such as severe liver, kidney dysfunction or cancer), and studies that only focused on subtypes of sRAGE. Reviews, letters, editorials, or case reports were also excluded. If the same population data were reported in multiple studies, only the one with the most detailed information and largest sample size was included, while the others were excluded.

The outcomes we sought for meta-analysis were means and standard deviations (SDs). If a publication reported medians and interquartile ranges (IQR), we used the approach proposed by Wan et al. [39] and Luo et al. [40] to estimate the means and SDs. Studies that did not provide means and SDs or other information that allowed for calculation of means and SDs were also excluded.

Data extraction

Two authors (Q.C. and W.K.) independently extracted data using a standardized spreadsheet. The following information was extracted from the included studies: first author, year of publication, country, patients' baseline information of DM Groups and Control Groups (sample size, patient type, DM duration, patient characteristics, percentage of male participants, age, BMI, HbA1C, sRAGE, and outcomes of interest). Any inconsistencies were resolved by discussion with a third author (L.Y.).

Quality assessment

The quality of evidence was rated using the Newcastle–Ottawa Scale [41]. The content of the assessment includes three domains: selection, comparability, and exposure. The detailed rules are listed in Supplementary Table S1. The scores range from 0 to 9 points, with 7 to 9 points indicating high quality, 5 to 6 points indicating medium quality, and 0 to 4 points indicating poor quality.

Statistical analysis

The means and SDs of the included studies were pooled using a random-effects meta-analysis. Outcome measures were calculated as the standardised mean difference (SMD), which was used to determine the magnitude of the effect, where <0.2, 0.2, 0.5, and 0.8 were defined as trivial, small, moderate, and large, respectively. Forest plots were drawn to intuitively visualize the means and SDs across studies for each outcome using a random-effects model. The Cochrane Q statistic and the I^2 statistic were calculated to evaluate heterogeneity across the included studies; $P<0.05$ was considered statistically significant, and the percentages of I^2 were categorized as 0–25%, 26–50%, 51–75%, and 76–100%, which were considered to be low, modest, moderate, and high probability of heterogeneity, respectively [42]. In addition, sensitivity analyses were performed by excluding studies one at a time to assess the influence of each individual study on the overall effect estimates. Funnel plots and Egger's test were used to evaluate publication bias. When publication bias was indicated, the trim-and-fill method was used to assess the stability of results. All analytical procedures were conducted with Review Manager (RevMan) Version 5.3 (The Cochrane Collaboration) and STATA version 17.0 (StataCorp, 4905 Lakeway Dr, College Station, TX 77845, USA).

Data and resource availability

All data relevant to the study are included in the article or uploaded as an additional file.

Results

Characteristics of the included studies

In total, 5947 potentially relevant publications were identified. Of these, 1759 duplicates were excluded. After screening the titles and abstracts, 123 studies were identified for further detailed evaluation. Eventually, 32 studies with 49 datasets [7–38] published between 2005 and 2024 were included in the final meta-analysis, involving a total of 4948 subjects, consisting of 811 subjects with type 1 diabetes and 4137 subjects with type 2 diabetes. A flowchart of this process is shown in Fig. 1.

The baseline characteristics of these subjects are illustrated in Table 1. 9 datasets from 8 studies [7, 8, 13, 18, 23, 24, 29, 31] included subjects with type 1 diabetes, while 40 datasets from 25 studies [9–17, 19–22, 25–28, 30, 32–38] focused on subjects with type 2 diabetes. Among them, 16 datasets [9–11, 15, 17, 20, 21, 27, 30, 32–35, 37, 38] were from type 2 diabetes subjects without any complications, of which 5 datasets [21, 27, 35, 37] were from newly diagnosed type 2 diabetes patients; 13 datasets [10, 15, 17, 20, 28, 30, 33, 34] were from type 2 diabetes subjects with complications, of which 5 datasets [17, 20, 28, 33] were from patients with diabetic nephropathy, 4 datasets [20, 28, 30, 33] from patients with diabetic retinopathy, 3 datasets [10, 15, 20] from patients with CVD, and 1 dataset [20] from patients with diabetic neuropathy. Additionally, 11 datasets did not provide detailed patient characteristics.

Among the studies, the sample sizes of the DM groups ranged from 15 to 1072, with average ages ranging from 12.69 to 70 years. The proportion of men in these groups ranged from 0 to 70.65%. The mean or median BMI ranged from 19.45 to 32.50 Kg/m^2. The mean HbA1C ranged from 6.15 to 10.47%. In the selected studies, the variation trend of sRAGE levels between the diabetes and healthy control groups was not consistent. In 13 datasets derived from 9 studies [9, 11, 21, 27, 32, 34, 36–38], sRAGE levels in subjects with diabetes were lower than those in the healthy group. In contrast, in 26 datasets from 17 studies [7, 8, 10, 13–20, 22, 23, 28, 30, 31, 33], sRAGE levels in subjects with diabetes were higher than those in the healthy group, while 10 datasets from 9 studies [12, 13, 17, 24–26, 29, 31, 35] showed no statistically significant difference between the two groups. For all included studies, the average Newcastle–Ottawa Scale scores ranged from 5 to 7, indicating medium to high methodological quality (Additional file: Supplementary Table S1).

Given that the included studies involved various populations (type 1 diabetes, type 2 diabetes with or without complications), we further analyzed sRAGE levels across different patient subgroups.

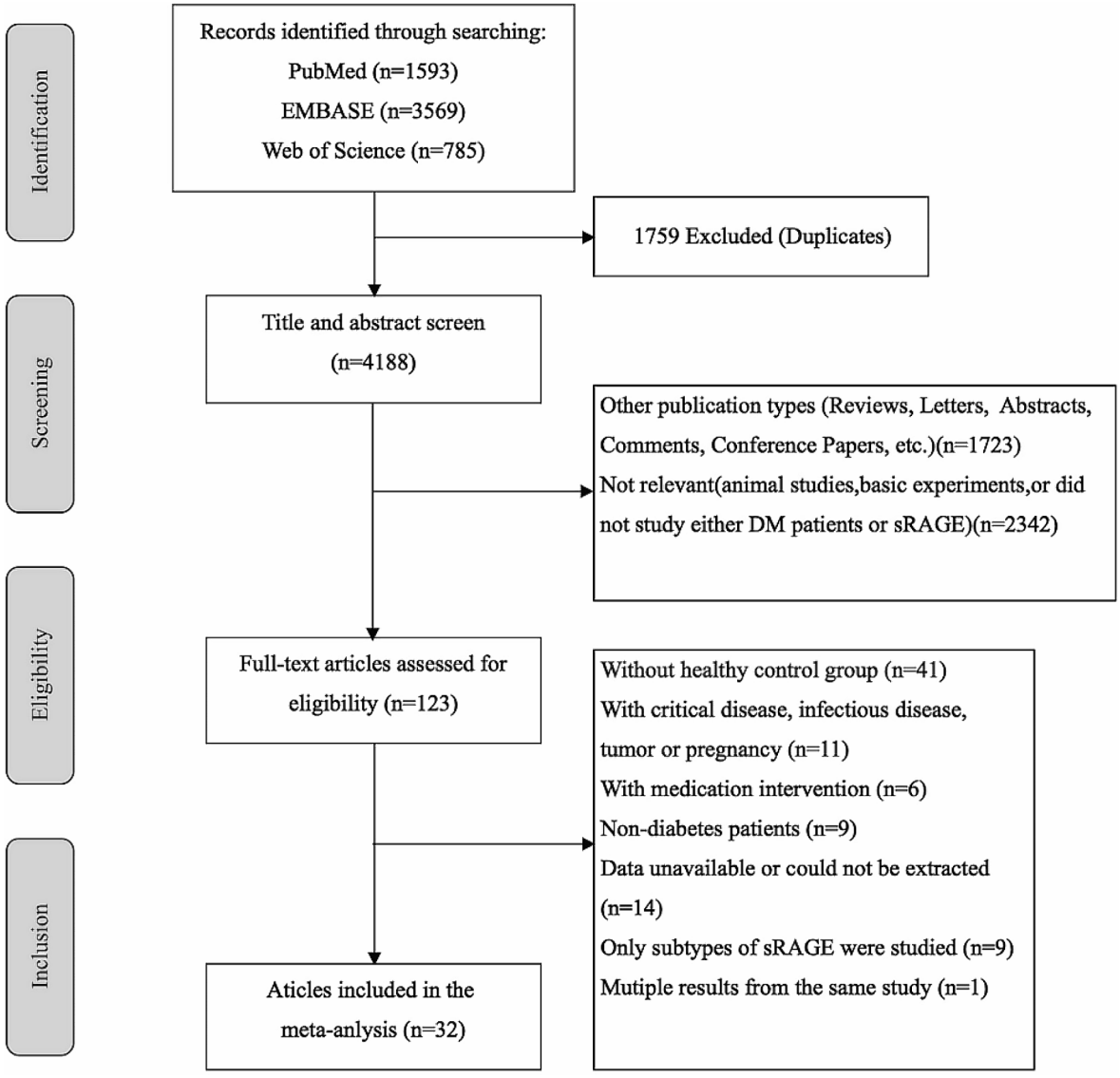

Fig. 1 Flowchart of the literature search and study selection

sRAGE in patients with type 1 diabetes

Data from 9 datasets across 8 studies [7, 8, 13, 18, 23, 24, 29, 31] focused on subjects with type 1 diabetes were pooled and analyzed. Compared with the healthy group, sRAGE levels in subjects with type 1 diabetes moderately but significantly increased (SMD 0.45, CI: 0.16–0.73), with high heterogeneity (I^2=79%, P=0.002). Following the exclusion of the study by Martin Heier [24], the I^2 statistic decreased from 79 to 30%. Considering the potential heterogeneity introduced by patient age, an age-stratified analysis was conducted for subjects with type 1 diabetes. Subjects aged 18 and above were classified as the adult group, while those under 18 were classified as the underage group. In the stratified subgroup analysis, sRAGE levels moderately but significantly increased in adult subjects with type 1 diabetes (SMD 0.48, CI: 0.31–0.65, I^2=0%, P<0.0001). In contrast, no statistically significant difference was observed between the underage subjects with type 1 diabetes and the healthy group (SMD 0.43, CI: -0.13-1.16, P=0.25) (Fig. 2).

sRAGE in patients with type 2 diabetes

Data from 40 datasets across 25 studies [9–17, 19–22, 25–28, 30, 32–38] on subjects with type 2 diabetes were pooled to analyze the difference in sRAGE levels. The difference in sRAGE levels between the total population with type 2 diabetes and the healthy group only reached borderline significance (SMD 0.40, CI: -0.02–0.83, I^2=99%, P=0.06). We conducted a subgroup analysis by stratifying the patients based on the presence or absence of diabetic complications. In individuals with diabetic complications, sRAGE was found largely and significantly

Table 1 Basic characteristics of eligible studies

Author	Year	Country	Study design	DM Groups									Control Groups					
				n	Type of patients	DM duration, y	Characteristic	Male, *n*(%)	Age, y	BMI, Kg/m^2	HbA1C (%)	sRAGE, pg/ml	*n*	Male, *n*(%)	Age, y	BMI, Kg/m2	HbA1C (%)	sRAGE, AU
Alan C H Lee [7]	2015	China	Cross-sectional study	102	T1DM	17.4 ± 9.1	None	40(39.22)	42.1 ± 11.1	23.1 ± 3.5	8.3 ± 1.4	999.29 ± 351.93	101	42(41.58)	43.2 ± 10.2	24.2 ± 3.4	5.4 ± 0.4	822.06 ± 449.00
Athina Dettoraki [8]	2009	Greece	Cross-sectional study	74	T1DM	NP	None	42(56.76)	13 ± 5	NP	8.0 ± 1.8	1430 ± 760	43	23(53.49)	13 ± 6	NP	NP	1158 ± 595
Eleonora Devangelio [9]	2007	Italy	Cross-sectional study	86	T2DM	5.5 (< 1–33)	None	42 (48.84)	62.9 ± 9.3	29 ± 4.1	7.9 ± 1.4	858.86 ± 334.78	43	22 (51.16%)	61.2 ± 9.1	22.9 ± 2.6	NP	1335.44 ± 562.18
Francesco Piarulli [10]	2022	Italy	Cross-sectional study	33	T2DM	NP	CVD	NP	65.5 ± 8.3	29.8 ± 3.9	7.0 ± 0.8	950 ± 500	27	NP	47.3 ± 13.4	25.5 ± 3.3	5.5 ± 0.4	310 ± 70
				31	T2DM	NP	None	NP	60.0 ± 5.9	29.2 ± 3.4	6.9 ± 0.8	620 ± 220 *						
Giuseppina Basta [11]	2006	Italy	Cross-sectional study	84	T2DM	NP	None	25(29.76)	60 ± 7	28.8 ± 3.5	7.3 ± 1.0	181.87 ± 220.26	76	23(30.26)	45 ± 10	28.0 ± 3.9	4.9 ± 0.4	752.63 ± 364.24
Ivan Raška Jr [12]	2017	Czech Republic	Cross-sectional study	112	T2DM	7.1 ± 6.5	25% osteoporosis, 8% low trauma vertebral, 19% non-vertebral fractures	0(0)	65.6 ± 9.4	32.5 ± 8.1	6.99 ± 3.63mmol/mol	1399.0 ± 624	171	0(0)	64.0 ± 9.5	26.8 ± 6.1	5.61 ± 2.51mmol/mol	1523.2 ± 613
J Skrha Jr [13]	2011	Czech Republic	Cross-sectional study	45	T1DM	18 (2–52)	NP	22(48.89)	47 (24–70)	25.9 ± 2.7	7.56 ± 1.32	1137 ± 532	43	29(67.44)	56 (25–60)	25.7 ± 3.9	3.60 ± 0.25	824 ± 309
				66	T2DM	9 (2–39)	NP	46(69.70)	64 (29–84)	29.0 ± 4.6	6.91 ± 2.18	995 ± 519 *						
Jacopo Sabbatinelli [14]	2022	Italy	Retrospective cohort study	362	T2DM	12.5 (6.0–24.0)	retinopathy, 26%; nephropathy, 15%; neuropathy, 20%; peripheral artery disease, 8%; MACE, 15%	200 (55%)	67.0 (60.0–72.0)	28.3 (25.9–31.4)	7.3 (6.5–8.1)	688.49 ± 346.17	125	59 (47%)	63.0 (56.0–73.5)	26.6 (24.0–29.2)	5.7 (5.5–6.1)	434.01 ± 240.68
Jie Li [15]	2020	China	Case-control study	22	T2DM	NP	None	10(45.45)	64.7 ± 3.9	27.6 ± 3.2	7.4 ± 0.7	470 ± 170	50	26(52.00)	65.6 ± 3.1	24.3 ± 2.6	6.1 ± 0.4	310 ± 110
				28		NP	Carotid atherosclerosis	11(39.29)				590 ± 210 *						
K Nakamura [16]	2007	Japan	Case-control study	86	T2DM	NP	NP	36 (41.86)	68.4 ± 9.6	24.7 ± 4.1	7.6 ± 1.4	515.5 ± 166	86	36 (41.86)	68.4 ± 8.9	23.2 ± 3.6	5.2 ± 0.4	391.3 ± 146
K. C. B. Tan [17]	2006	China	Cross-sectional study	110	T2DM	12.1 ± 6.4	Normoalbuminuria	53(48%)	51.4 ± 6.9	25.3 ± 3.9	8.6 ± 1.6	978.83 ± 447.64	150	75(50.00)	51.0 ± 5.8	24.6 ± 3.3	5.6 ± 0.5	1026.00 ± 463.20
				108	T2DM	10.8 ± 7.6	Microalbuminuria	57(53%)	53.3 ± 8.9	26.4 ± 3.9	8.3 ± 1.2	1045.96 ± 407.10 *						
				100	T2DM	10.4 ± 5.8	Proteinuria	66(66%)	54.2 ± 9.9	26.7 ± 4.5	8.6 ± 1.8	1247.07 ± 631.18 †						
Karolina Nocuń-Wasilewska [18]	2021	Poland	Prospective cohort study	66	T1DM	3.8 ± 4.2	NP	35(53.03)	12.69 ± 3.6	19.45 ± 3.9	10.47 ± 3.07	380.20 ± 282.90	21	5(23.81)	9.26 ± 2.9	17.47 ± 2.7	NP	84.94 ± 2.27
Kazuo Nakamura [19]	2006	Japan	Case-control study	75	T2DM	NP	13.33% CAD	29 (38.6%)	66.2 ± 10.2	24.9 ± 4.2	7.8 ± 1.6	965.3 ± 544.2	75	29 (38.67)	66.2 ± 11.5	23.3 ± 3.7	5.2 ± 0.3	415.7 ± 150.4

Table 1 (continued)

Author	Year	Country	Study design	DM Groups									Control Groups					
				n	Type of patients	DM duration, y	Characteristic	Male, *n*(%)	Age, y	BMI, Kg/m^2	HbA1C (%)	sRAGE, pg/ml	*n*	Male, *n*(%)	Age, y	BMI, Kg/m2	HbA1C (%)	sRAGE, AU
Krishna A. Adeshara [20]	2022	India	Cross-sectional study	200	T2DM	9.64 ± 5.93	None	104(52.00)	55.6 ± 9.79	NP	7.96 ± 2.41	1619 ± 538.6	103	60(58.25)	52.04 ± 8.95	NP	5.02 ± 0.74	587.0 ± 237.8
				33	T2DM	9.35 ± 3.46	Diabetic retinopathy	14(42.42)	60.66 ± 8.04	NP	8.85 ± 2.20	1396 ± 723.1 *						
				80	T2DM	9.12 ± 2.96	Diabetic nephropathy	28(35.00)	58.0 ± 10.9	NP	9.51 ± 2.26	2062 ± 652.1 †						
				37	T2DM	9.10 ± 3.18	Diabetic neuropathy	7(23.33)	59.40 ± 5.19	NP	7.56 ± 1.77	1053 ± 385.4 ‡						
				50	T2DM	8.29 ± 2.94	CAD	19(38.00)	58.32 ± 9.87	NP	7.99 ± 1.13	1134 ± 595.2 §						
Liangkai Chen [21]	2024	China	Case-control study	1072	T2DM	NP	New-onset	600 (55.97%)	54.0 ± 9.3	25.1 ± 3.5	NP	898.88 ± 410.13	1072	600 (55.97)	53.9 (10.2)	23.6 (3.0)	NP	1252.67 ± 600.23
				127	T2DM	NP	New-onset	91 (71.65%)	62.2 (5.1)	24.2 (3.2)	NP	968.48 ± 454.95 *	381	273 (71.65)	62.2 (5.1)	23.7 (3.0)	NP	1117.68 ± 546.95
Magdalena Kopytek [22]	2020	Poland	Cross-sectional study	50	T2DM	11 (7–18)	Aortic stenosis	31 (62)	70 (66–74)	31.3 (28.7–34.5)	6.8 (6.3–7.8)	2040.75 ± 836.58	76	41 (53.9)	68 (66–72)	28.4 (26.6–31.2)	5.4 (5.2–5.7)	823.8 ± 244.09
Marion Challier [23]	2005	France	Cross-sectional study	45	T1DM	14 ± 11	20% Diabetic retinopathy	NP	40 ± 15	NP	8.5 ± 1.7	1320 ± 459	35	NP	43 ± 10	NP	NP	1041 ± 392
Martin Heier [24]	2015	Norway	Prospective cohort study	299	T1DM	NP	NP	149 (49.8)	13.7 ± 2.8	20.8 ± 3.9	8.4 ± 1.2	1664 ± 602	112	48(42.9)	13.4 ± 2.5	19.2 ± 3.1	5.3 ± 0.3	1773 ± 574
Mattabhorn Phimphilai [25]	2017	Thailand	Cross-sectional study	27	T2DM	10.9 ± 7.7	Diabetic microvascular complications 59.3%;Diabetic macrovascular complications22.2%	9(33.3)	63.9 ± 7.2	NP	7.6 ± 1.6	541.7 ± 232.3	15	3(20.00)	61.8 ± 9.0	NP	NP	488.1 ± 241.0
Mattabhorn Phimphilai [26]	2021	Thailand	Cross-sectional study	40	T2DM	NP	47.5% Microvascular complication, 10% Macrovascular complications	16(40.00)	58.1 ± 6.8	25.8 ± 4.3	7.5 ± 0.9	527.1 ± 249.7	30	11(36.67)	59.7 ± 7.7	24.6 ± 3.9	5.9 ± 0.50	599.4 ± 422.1
Minglian Huang [27]	2015	China	Cross-sectional study	30	T2DM	NP	New-onset	13(43.33)	51.3 ± 10.49	26.02 ± 3.74	6.82 ± 0.85	590 ± 160	30	13(43.33)	47.6 ± 11.91	24.32 ± 3.82	5.54 ± 0.39	748 ± 180
Mohsen Kerkeni [28]	2012	Tunisia	Prospective cohort study	100	T2DM	16.8 ± 9.6	Diabetic nephropathy	106(53)	57 ± 12	30.4 ± 3.4	8.2 ± 2.7	200.63 ± 48.83	30	17(56.67)	52 ± 9	5.6 ± 0.2	NP	148.72 ± 32.73
				100	T2DM		Diabetic retinopathy					206.45 ± 53.18 *						
Naoto Katakami [29]	2008	Japan	Cross-sectional study	130	T1DM	13.6 + 6.7	None	49(37.69)	23.6 + 4.9	22.5 + 2.6	7.79 + 1.44	1505 + 599	22	9(40.91)	25.7 + 3.8	20.5 + 1.8	4.66 + 0.25	1314 + 474
Ning Dong [30]	2015	China	Prospective cohort study	113	T2DM	8.7 ± 7.2	None	59(52.21)	66.2 ± 8.4	24.8 ± 5.8	7.7 ± 1.2	293.81 ± 112.91	108	62(57.41)	66.8 ± 8.8	24.7 ± 5.2	5.5 ± 0.3	137.87 ± 66.44
				151	T2DM	11.8 ± 5.9	Diabetic retinopathy	83(54.97)	66.7 ± 8.1	25.1 ± 5.5	8.2 ± 1.8	335.50 ± 180.68 *						
S F Bakker [31]	2015	Netherlands	Case-control study	25	T1DM	30 ± 14	Crohn disease	9(36.00)	53 ± 16	24.7 ± 4.3	7.39 ± 3.03	1395 ± 467	25	5(20.00)	49 ± 9	24.3 ± 3.5	NP	1309 ± 400
				25	T1DM	29 ± 14	None	10(40)	55 ± 15	24.1 ± 3.4	7.89 ± 3.33	1554 ± 449 *						

Table 1 (continued)

Author	Year	Country	Study design	DM Groups								Control Groups					
				n	Type of patients	DM duration, y	Characteristic	Male, *n*(%)	Age, y	BMI, Kg/m^2	HbA1C (%)	sRAGE, pg/ml	*n*	Male, *n*(%)	Age, y	BMI, Kg/m2	HbA1C (%)	sRAGE, AU
Sandeep Singhal [32]	2016	India	Cross-sectional study	20	T2DM	NP	Chronic periodontitis	11(55)	39.0 ± 4.14	NP	6.705 ± 0.17	460.23 ± 81.23	15	7(46.67)	33.6 ± 6.27	NP	4.59 ± 0.38	732.88 ± 68.97
				15	T2DM	NP	None	7(46.66)	33.6 ± 6.27	NP	6.800 ± 0.18	555.99 ± 83.53 *						
Shazia Qayyum [33]	2021	Pakistan	Case-control study	150	T2DM	9.31 ± 4.01	None	65	58.16 ± 9.42	NP	NP	582.04 ± 206.04	150	67(67.00)	55.90 ± 10.90	NP	NP	164.05 ± 70.53
				150	T2DM	13.02 ± 5.71	Diabetic retinopathy	63	56.25 ± 8.56	NP	NP	600.12 ± 38.54 *						
Sinan Subhi Farhan [34]	2019	Iraq	Cross-sectional study	25	T2DM	3.2 ± 1	None	13 (52.00)	55.8 ± 4.1	NP	6.7 ± 0.4	912.8 ± 294.3	20	10(50.00)	56.8 ± 3.9	NP	4.3 ± 0.2	1718.3 ± 455.7
				25	T2DM	6.7 ± 0.9	Reno-vascular complication	14 (56.00)	55.6 ± 4.2	NP	7.9 ± 0.7	868.7 ± 50.8 *				NP		
Subrata Kumar Biswas [35]	2015	Bangladesh	Cross-sectional study	66	T2DM	NP	New-onset	31(46.97)	42.5 ± 8.4	25.4 ± 4.6	8.1 ± 2.4	652.35 ± 245.56	40	18(45.00)	38.4 ± 7.6	25.9 ± 6.2	5.0 ± 0.4	634.87 ± 346.79
Tarek Mk Motawi[36]	2013	Egypt	Cross-sectional study	28	T2DM	7.82 ± 0.76	GCD	13(46.43)	56.39 ± 1.43	31.72 ± 0.77	6.15 ± 0.10	630.47 ± 48.14	20	8(40.00)	51.25 ± 1.51	30.00 ± 0.82	5.26 ± 0.08	804.92 ± 58.14
				42	T2DM	10.48 ± 1.01	PCD	10(23.81)	54.00 ± 1.17	32.02 ± 0.52	8.71 ± 0.57	600.06 ± 37.75 *						
Xu-Dong Su [37]	2011	China	Case-control study	50	T2DM	NP	New-onset	27 (54.00%)	52 ± 7.7	27.6 ± 0.7	8.53 ± 0.58	573.6 ± 172.5	50	26 (52.00)	51 ± 6.5	24.4 ± 0.5	5.0 ± 0.4	603.4 ± 120.8
Xystus H L Tam [38]	2011	China	Case-control study	53	T2DM	13 (7–16.5)	None	23(43.40)	52.6 ± 1.3	27.6 ± 0.7	9.74 ± 0.25	567.43 ± 288.51	52	25(48.98)	51.6 ± 0.9	24.4 ± 0.5	NP	654.05 ± 408.29

Continuous data are presented as as mean ± SD or medians (interquartile range), and categorical data are presented as *N* (%)

DM: diabetes mellitus; T1DM: type 1 diabetes; T2DM: type 2 diabetes; CAD: coronary artery disease; GCD: good controlled diabetic patients; PCD: poorly controlled diabetic patients; NP: not provided; MACE: major adverse cardiovascular events

UP: sRAGE in DM Group is higher than that in Control Group; DOWN: sRAGE in DM Group is lower than that in Control Group; NS: **no significant difference is in** DM Group and Control Group

*, †, ǂ, §: used to distinguish multiple datasets in one study

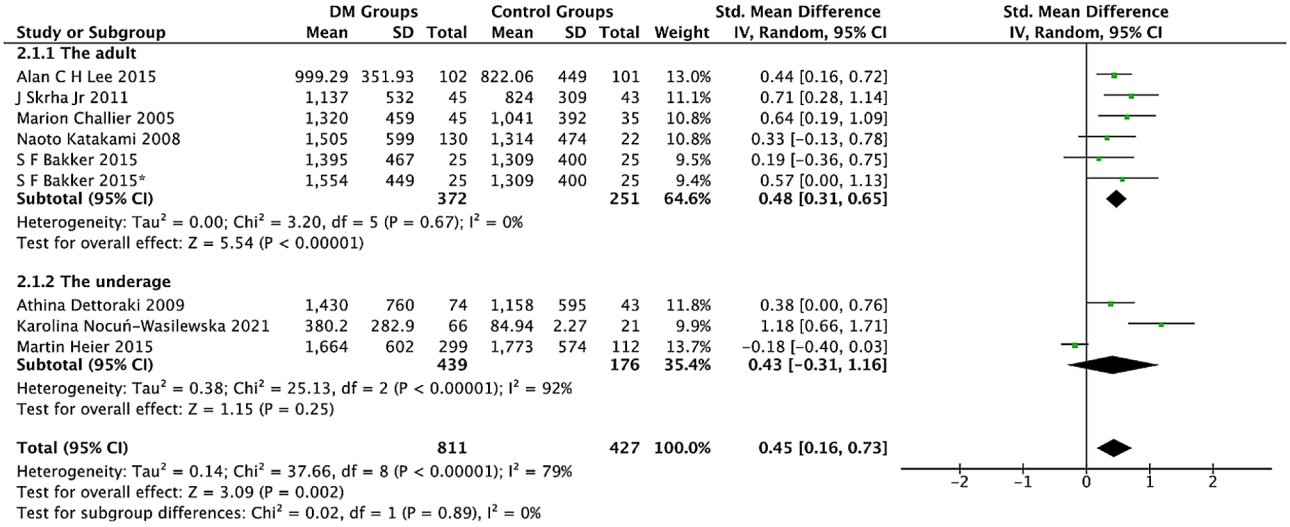

Fig. 2 sRAGE in subjects with type 1 diabetes stratified by age (the adult and the underage) [SMDs were pooled using random-effects meta-analysis]

higher than that in the healthy group (SMD 1.59, CI: 0.77–2.41, P=0.0001). There was no significant difference between individuals without complications and the healthy group (SMD 0.01, CI: -0.61–0.64, P=0.97). Substantial heterogeneity was detected in these studies. (Fig. 3).

Subsequent subgroup analyses were conducted on patients with different types of diabetic complications and those newly diagnosed with type 2 diabetes. Compared with the healthy group, large and significant increases in sRAGE were observed in subjects with diabetic retinopathy (SMD 3.02, CI: 0.83–5.21, P=0.007), CVD (SMD 1.56, CI: 1.28–1.83, P<0.00001)and diabetic neuropathy (SMD 1.63, CI: 1.21–2.06, P<0.00001). No significant difference was found in sRAGE levels of subjects with type 2 diabetes nephropathy (SMD 0.44, CI: -0.76–1.64, P=0.47). Significant heterogeneity has also been found in studies on diabetic nephropathy and retinopathy. (Fig. 4)

Five datasets were derived from 4 studies [21, 27, 35, 37] that focused on subjects with newly diagnosed type 2 diabetes. sRAGE levels were moderately but significantly lower in subjects with newly diagnosed diabetes than those in the healthy control group (SMD-0.40, CI: -0.71–-0.09, I^2=86%, P=0.01). (Fig. 5)

Sensitivity analysis

Sensitivity analysis was performed by excluding individual studies one at a time to detect the impact of each individual dataset on the pooled SMD. For type 1 diabetes, the pooled SMD estimates did not change significantly by excluding any individual study in either range or direction (Additional file: Supplementary Figure S1). sRAGE in the overall type 2 diabetes population exhibited a modest effect size of 0.40, with a confidence interval ranging from −0.02 to 0.83. Following the exclusion of certain studies [9, 11, 32, 34, 36], the pooled SMD estimates showed a significant effect size, indicating that sRAGE levels in subjects with type 2 diabetes were greater than those in healthy individuals. In the subgroup analysis of type 2 diabetes subjects with and without complications, after excluding individual study one at a time, the pooled SMD estimates remained consistent and robust. (Additional file: Supplementary Figure S2 and S3)

Publication bias

Funnel plots assessing publication bias are shown in the Supplementary Materials. The funnel plot for type 1 diabetes (Additional file: Supplementary Figure S4) suggested publication bias, which was further corroborated by Egger's test (P=0.023). Utilizing the trim-and-fill method in the random-effects model, the outcome showed no substantial variation after incorporating 4 additional studies (SMD: 1.190, CI: 0.893–1.584). The direction of the results remained consistent with the original findings, indicating outcome stability (Additional file: Supplementary Figure S5). For subjects with type 2 diabetes, the funnel plots were symmetrical both in the overall population and in subgroups with or without complications. Egger's test showed P=0.055, P=0.623, and P=0.137, respectively (Additional file: Supplementary Figure S6).

Discussion

To the best of our knowledge, this is the first study to comprehensively analyze the sRAGE levels in patients with type 1 and type 2 diabetes. Interestingly, we found that changes in sRAGE levels among diabetes patients vary across different types and stages of the disease. This may be because sRAGE levels in diabetes patients are

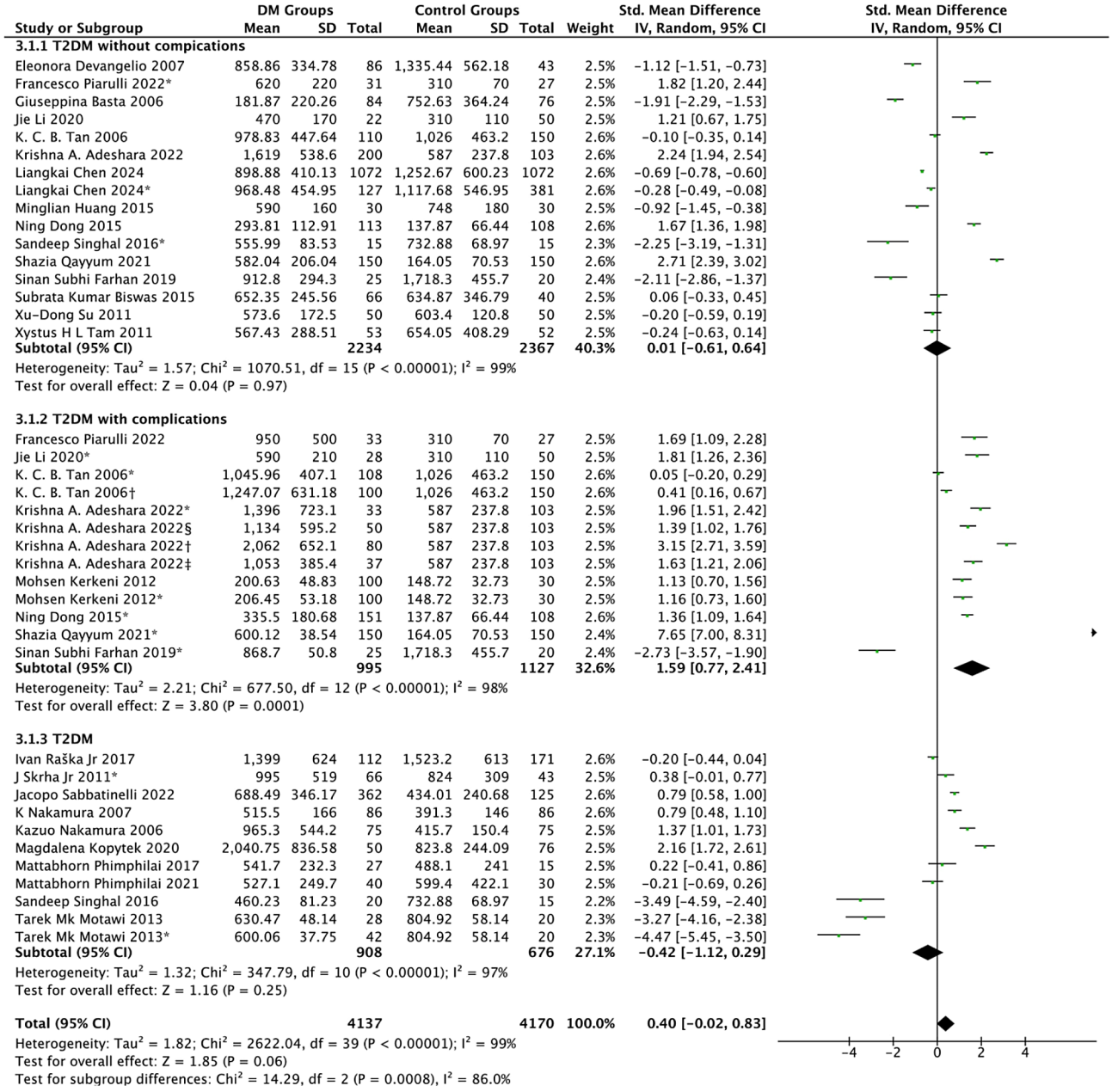

Fig. 3 sRAGE in subjects with type 2 diabetes stratified by complications (type 2 diabetes with complications and type 2 diabetes without complications) [SMDs were pooled using random-effects meta-analysis]

regulated by multiple factors, including genes and the internal environment.

Firstly, the greatest genetic risk for type 1 diabetes is conferred by two chromosomal loci, HLA class II and variable tandem repeats in the insulin gene region [43]. sRAGE concentrations decrease in carriers of the HLA DR3/DR4 and the DR3 allele, while the HLA-DR4/non-DR3 genotype is associated with increased sRAGE concentrations [44]. The AGE-specific receptor gene (AGER), encoding RAGE, is located on the short arm of chromosome 6 within the HLA class III region, near the junction with class II loci [45]. Three single nucleotide polymorphisms (SNPs) of the AGER gene (rs2070600, rs9469089, and rs17493811) are associated with an increased risk of type 1 diabetes, of which rs2070600 is associated with decreased sRAGE concentrations, while rs9469089 is linked to increased concentrations [44]. Obviously, the AGER and/or HLA class II genotype can regulate sRAGE concentrations in patients with type 1 diabetes. Secondly, sRAGE consists of esRAGE and cRAGE, with cRAGE accounting for over 75%, which is proteolytically cleaved from fl-RAGE via MMPs. AGEs

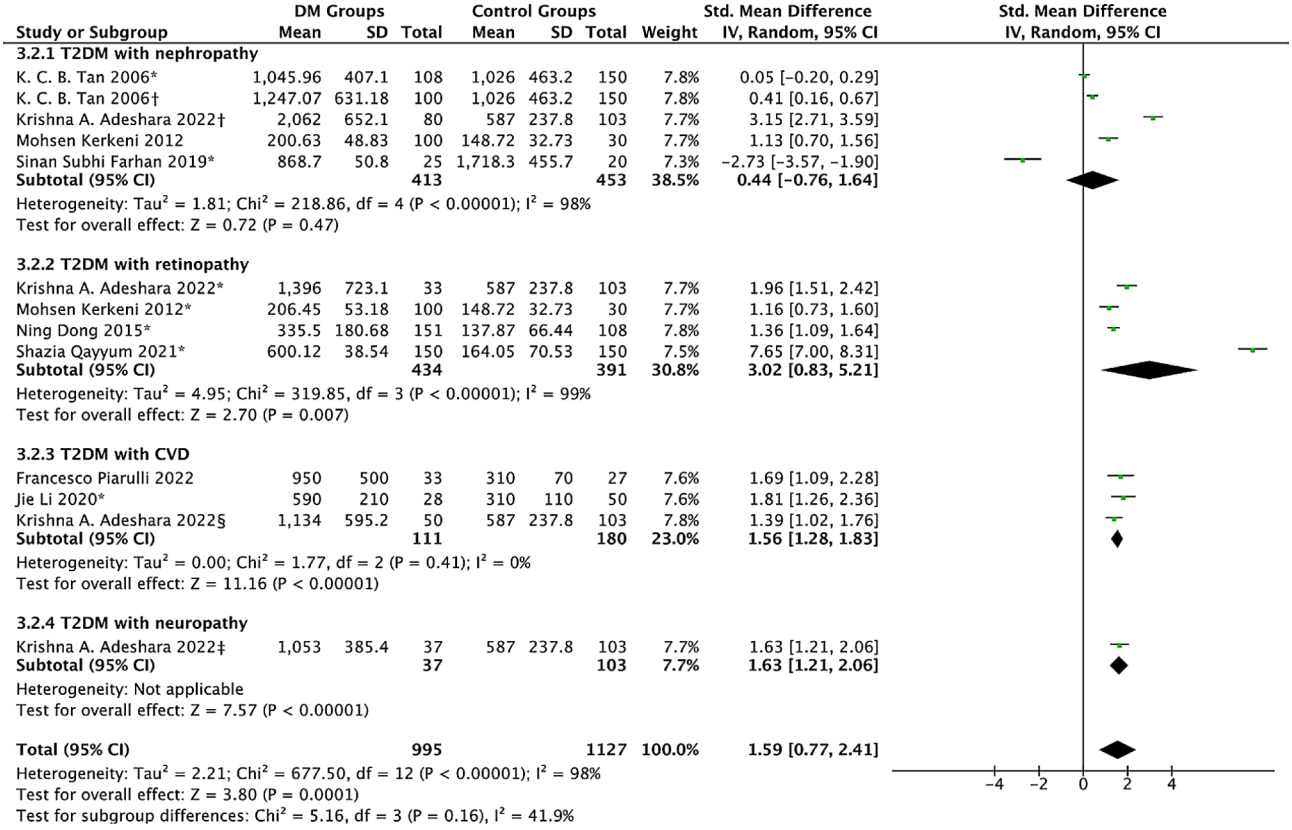

Fig. 4 sRAGE in type 2 diabetes with complications stratified by the type of complications (diabetic nephropathy, diabetic retinopathy, diabetic CVD, and diabetic neuropathy) [SMDs were pooled using random-effects meta-analysis]

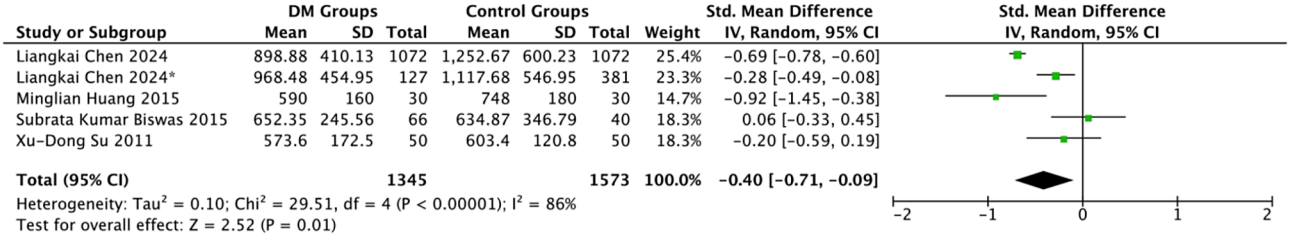

Fig. 5 sRAGE in subjects with newly diagnosed type 2 diabetes [SMDs were pooled using random-effects meta-analysis]

increase in diabetes patients, which can upregulate the expression of fl-RAGE and MMPs. Additionally, hyperglycemia-induced ROS is known to enhance the expression and activity of MMPs. These factors can lead to an increase in sRAGE levels [1]. Finally, in addition to AGEs, the binding of other ligands(such as S100A12)to RAGE can also affect changes in sRAGE levels [11].

Our meta-analysis revealed that sRAGE levels in subjects with type 1 diabetes increased, particularly in adult subjects, with no similar trend observed in underage subgroups. These factors may have contributed to the observed differences. First, HLA DR3/DR4 heterozygotes and DR3 allele are susceptible genotypes for type 1 diabetes, with the former carrying the highest genetic risk and both being associated with decreased sRAGE levels. High-risk gene carriers may develop type 1 diabetes with decreased sRAGE levels at an earlier age; in other words, the decreased sRAGE levels in type 1 diabetes may reflect a more aggressive disease phenotype, especially in younger patients [44]. Second, in individuals with chronic stable conditions characterized by autoimmunity and inflammation, compensatory mechanisms may be activated as the disease progresses, leading to elevated circulating protective sRAGE. It is possible that the increase in sRAGE observed in the adult group is a result of these compensatory mechanisms. Finally, insulin therapy is the primary treatment option for patients with type 1 diabetes to regulate blood glucose levels. Insulin therapy not only increases the expression of fl-RAGE and esRAGE but also stimulates the detachment of sRAGE from

membrane-bound receptors [46]. The authors speculated that the adult patients have a longer course of disease and longer duration of insulin use, which may contribute to the increase in sRAGE levels.

sRAGE levels in type 2 diabetes with complications were significantly higher, while no statistically significant elevation was observed in subjects without complications. There are several possible explanations. First, similar to type 1 diabetes, the elevation of sRAGE levels may be a compensatory response to hyperglycemia, inflammation, and oxidative stress. As diabetes progresses, AGEs persistently accumulate, exacerbating hyperglycemia-induced inflammation and target organ damage and increasing the expression of RAGE in different cell types [9]. AGEs, inflammation and ROS promote the upregulation of factors (such as MMP9) that lead to the shedding of RAGE extracellular domains, resulting in an increase in sRAGE levels [47]. Second, the increase in sRAGE levels may also be related to the concomitant medications used by patients. Clinical research has confirmed that sRAGE increases significantly after 12 weeks of treatment with oral hypoglycemic drugs or insulin in newly diagnosed type 2 diabetes subjects [9]. Not only insulin, but also medications such as thiazolidinediones [48], statins [49], and ACEI [50] have been shown to stimulate the production of sRAGE. Interestingly, we did not observe a significant result in subjects without complications. The damage of target organs may be an important factor affecting the sRAGE levels in patients with type 2 diabetes. Nevertheless, the specific mechanisms require further experimental clarification.

Unlike patients with complications of type 2 diabetes, newly diagnosed type 2 diabetes patients have reduced sRAGE levels compared to healthy individuals. However, the underlying mechanism remains unclear. It is speculated that this decrease may be attributed to the increased production of AGEs under hyperglycemic conditions, where sRAGE competes with RAGE for binding to AGEs. Consequently, levels of free sRAGE are reduced, and the clearance rate of the AGE ligand/sRAGE complex increases, leading to a reduction in sRAGE [51]. Meanwhile, S100A12, another ligand of RAGE, is negatively correlated with sRAGE levels. Insulin resistance may upregulate S100A12 release in diabetes patients, which in turn decreases sRAGE levels [11].

Obviously, our research has clarified the sRAGE levels of diabetes patients in different types and stages, which provides a reference for future researchers, but it also has some limitations. First, in the included studies, both subjects and healthy individuals showed significant variability in sRAGE levels. At present, there is no standard value for sRAGE level that can be used as a reference. It may be a source of heterogeneity in various analyses. So, a standardized detection method for sRAGE is urgently needed to be designed and standardized. Second, our analysis included some cross-sectional studies, and each experiment may introduce some degree of experimental bias, which could be a source of moderate to high heterogeneity in some outcomes. Third, some studies had relatively small sample sizes, which could have affected the accuracy of our results. Finally, some sRAGE data could not be directly extracted; although we calculated the data based on the references, bias might not be completely avoided.

Conclusion

In conclusion, our results indicate that the changes in sRAGE levels in patients with diabetes were not uniform. sRAGE was found to be higher in type 1 diabetes patients and type 2 diabetes patients with complications; no significant change was observed in type 2 diabetes patients without complications. Additionally, sRAGE decreased in patients with newly diagnosed type 2 diabetes. Further research is necessary to understand the underlying mechanisms of these changes in sRAGE levels in patients with diabetes.

Abbreviations

AGEs	Advanced glycation end products
RAGE	Receptor for advanced glycation end products
sRAGE	Soluble receptors for advanced glycation end products
T1DM	Type 1 diabetes
T2DM	Type 2 diabetes
DM	Diabetes mellitus
SD	Standard deviation
CVD	cardiovascular disease
AGER	AGE-specific receptor

Supplementary Information

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Supplementary Material 1

Author contributions

Study concept and design: Q.C, L. L, Y. L. Acquisition of data: Q. C, W. K, X. L. Analysis and interpretation of data: Q. C, L. L W. K. Statistical analysis: Q.C, L. L. Wrote the first draft of the manuscript: Q. C, L. L, W. K. Critical revision of the manuscript for important intellectual content: H. X, Y. L. Supervision: Y. L. All authors read and approved the final manuscript. Qimou Chen, Liehua Liu, and Weijian Ke contributed equally to the manuscript.

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Data availability

All data relevant to the study are included in the article or uploaded as an additional file.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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