

The association of oxidative stress biomarkers with type 2 diabetes mellitus: a systematic review and meta-analysis

Sujan Banik (✉ pharmasujan@yahoo.com)

Noakhali Science and Technology University Faculty of Pharmacy <https://orcid.org/0000-0001-9639-6836>

Antara Ghosh

Noakhali Science and Technology University Faculty of Pharmacy

Systematic Review

Keywords: Type 2 diabetes mellitus, glutathione peroxidase, malondialdehyde, superoxide dismutase, total antioxidant status

Posted Date: April 12th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-319443/v1>

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Version of Record: A version of this preprint was published at Health Science Reports on October 1st, 2021. See the published version at <https://doi.org/10.1002/hsr2.389>.

Abstract

Purpose: Although the exact etiologies of type 2 diabetes mellitus (T2DM) are not well defined, the effect of oxidative stress is considered an important factor in the development of T2DM. However, there are controversial outcomes in the association between oxidative stress biomarker levels and T2DM. The present study was aimed to critically examine the association of oxidative stress biomarkers with T2DM.

Methods: We systematically searched different electronic databases like PubMed, Google Scholar, ScienceDirect, and Web of Science to find relevant articles up to 31 December 2019. The pooled standard mean difference (SMD) with a 95% confidence interval (CI) was used to define the variation between the study groups.

Results: A total of 22 case-control studies with 2853 subjects (1667 diabetic patients and 1186 healthy controls) were selected for this meta-analysis. The pooled results of meta-analysis showed a significant difference in the malondialdehyde (MDA) levels [SMD (95% CI): 2.27 (1.62, 2.91)], nitric oxide (NO) levels [SMD (95% CI): 1.40 (0.00, 2.81)], glutathione (GSH) levels [SMD (95% CI): -1.76 (-2.94, -0.59)], and total antioxidant status (TAS) levels [SMD (95% CI): -1.40 (-2.28, -0.51)] between patients group and controls. Whereas, there was no significant difference observed in the superoxide dismutase (SOD) levels [SMD (95% CI): -1.20 (-2.55, 0.15)] and glutathione peroxidase (GPX) levels [SMD (95% CI): 0.07 (-2.80, 2.94)].

Conclusion: The current meta-analysis suggests that oxidative stress might have a potential role in the pathogenesis of T2DM in humans. Further studies should be needed to elucidate the possible mechanism and strengthen this evidence.

1. Introduction

Diabetes mellitus (DM) is a group of metabolic disorders characterized by elevated levels of glucose in the blood and insufficient secretion or action of endogenous insulin. A report by the International Diabetes Federation in 2017, the worldwide prevalence of diabetes in the adult population reached 8.8% (424.9 million people) [2]. Among them the majority (87%-91%) of the cases with type 2 diabetes. Type 2 diabetes mellitus (T2DM) is considered a major public health concern globally due to its life-threatening complications. It decreases the quality of life and increases the risk of mortality [3]. Although the exact etiologies of T2DM are not well defined, it's believed that autoimmune disease, genetic, and environmental factors play a major role in the development of T2DM [4]. Also, recent studies have shown that oxidative stress plays a significant role in the development and progression of T2DM [5–8].

Oxidative stress (OS) can be defined as an imbalance between the production of reactive oxygen species (ROS) and the ability of the body to detoxify its harmful effects through antioxidants. An excess formation of ROS such as superoxide, hydrogen peroxide, and hydroxyl radicals can cause harmful effects on important cellular structures like protein, lipids, and nucleic acids [9]. Antioxidants like catalase (CAT), superoxide dismutase (SOD), glutathione (GSH), and glutathione peroxidase (GPX) counter the action of ROS by neutralizing their action or by inhibiting their formation [10]. Thus, a balance might be important between ROS and the levels of the antioxidant, otherwise, OS has been implicated in the pathogenesis of a variety of diseases, including cancer and heart disease [11]. Various studies have reported a significant and abnormal increase in the levels of OS biomarkers in T2DM [12–33]. Moreover, Lipiski et al. [34] reported that the decreased levels of enzymatic antioxidants in T2DM leading to the development of diabetic complications. However, the results are controversial.

Therefore, our purpose of the present study was to systematically review the evidences of published case-control studies on this topic and performing meta-analysis of the results to summarize and delineate the association between OS and T2DM.

2. Methods

2.1 Literature search strategy

We performed this systematic review on oxidative stress in diabetes mellitus according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [35]. To find relevant peer-reviewed studies regarding the levels of oxidative stress markers, antioxidants status in diabetes mellitus, mainly four diverse search engines like PubMed, Google Scholar, ScienceDirect, and Web of Science were used. The search term included 'type 2 diabetes mellitus', 'T2DM', 'MDA', 'malondialdehyde', 'oxidative stress', 'antioxidants', 'total antioxidant capacity', 'total antioxidant status', 'superoxide dismutase', 'glutathione', 'glutathione

peroxidase', 'nitric oxide', 'catalase', 'vitamin A', 'vitamin C', and 'vitamin E'. The combinations of different search terms were used for identifying the relevant articles, and the search strategies were customized to suit each database.

2.2 Criteria for inclusion and exclusion

Inclusion criteria for this study were 1) study must be a case-control study design; 2) published in a peer-reviewed journal in the English language; 3) assessment of OS biomarkers and antioxidant status should be available in both patients and control subjects; 4) studies have clear diagnostic criteria; and 5) reported studies were available in full text (not editorial, commentary, or abstract for conferences). Studies were excluded if 1) published in other languages than English and contained only qualitative data; 2) no healthy control subjects; 3) subjects have any history of other diseases.

2.3 Data extraction and management

Both authors independently performed data extraction using standard extraction spreadsheets from the selected articles based on the inclusion criteria and enlisted in a table. The following items were extracted from each study: author's name (first author), year of publication, country, groups, gender distribution, mean age (years), number of participants (male vs female), MDA concentration, SOD concentration, GSH concentration, GPX concentration, CAT concentration, TAS concentration, and NO concentration. After the extraction of the data, the authors cross-checked the data tables and resolved any conflicts and inconsistencies during the data extraction process through discussion with each other.

2.4 Quality assessment

The quality assessment of all included studies was conducted by using a modified Newcastle-Ottawa Quality Assessment scale and we adopted three main criteria for selecting the studies in this systematic review: a) an appropriate and clear study objective/research question/aim; b) a detailed description of the study population with a valid methodology; and c) applicability of results.

2.5 Statistical analysis

A statistical software named Review Manager V5.3 (Cochrane Collaboration, Copenhagen, Denmark) was used for the meta-analysis. We calculated the standard mean difference (SMD) with a corresponding 95% confidence interval (CI) for each parameter using the random-effects model. The SMD was calculated as the ratio of the mean difference to the pooled standard deviation by the z-test. The existence of heterogeneity among studies was evaluated using I^2 and its resultant p -value using chi-squared tests. A value of I^2 25%, 50%, and 75% was used to define the heterogeneity as low, medium, and high heterogeneity. The random-effect model and forest plots were adopted as the pooling method, and funnel plots were used to investigate the publication bias. A p -value < 0.05 was considered a statistically significant difference between groups.

3. Results

3.1 Search results

As shown in Fig. 1, a total of 483 studies initially were identified through different database searching. After the removal of duplication, additional screening, and analysis of the titles and abstracts, 33 articles were included as eligible for this study. Out of 33 articles, finally, 22 studies were included in the qualitative and quantitative review and meta-analysis in the study.

3.2 Characteristics of included studies

The main characteristics of the included studies published between 1993 and 2018 with 2853 participants (1667 type 2 diabetic patients and 1186 healthy controls) are summarized in Table 1. The studies were conducted in India (n = 9), Turkey (n = 4), China (n = 2), Egypt (n = 2), France (n = 1), Sweden (n = 1), Thailand (n = 1), UAE (n = 1), and Bangladesh (n = 1). All studies included both men and women, except in four studies, there was no information about the sex of participants [15,21,26,30]. Studies were evaluated different biomarkers to evaluate the oxidative stress in the patient group compared to control subjects. Among the 22 studies, based on different types of OS biomarkers (MDA/TAS/GPX/GSH/NO/SOD), studies were categorized into the following six groups:

1. A total of 21 studies [12–33] reported the association between MDA levels and T2DM (1362 cases and 1168 controls) (Table 2),

2. A total of 8 studies [15,18–22,26,30] reported the association between SOD levels and T2DM (493 cases and 450 controls) (Table 2),
3. A total of 6 studies [12,15,18–20,26] reported the association between GSH levels and T2DM (382 cases and 327 controls) (Table 2),
4. A total of 4 studies [15,18,21,30] reported the association between GPX levels and T2DM (306 cases and 288 controls) (Table 2),
5. A total of 5 studies [17,22,29,31] reported the association between TAS levels and T2DM (376 cases and 359 controls) (Table 2), and
6. A total of 4 studies [19,31–33] reported the association between NO levels and T2DM (217 cases and 176 controls) (Table 2).

3.3 Association between MDA and T2DM

There were 21 studies to be included in the meta-analysis to evaluate the overall effect of MDA in T2DM. Based on the random-effects modeling of meta-analysis, significantly higher levels of serum MDA were observed in the patient group compared to the control subjects [SMD (95% CI): 2.27 (1.62, 2.91), $z = 6.90$, $p < 0.00001$]. We found a significant level of heterogeneity for MDA among the existing studies ($I^2 = 98\%$, $p < 0.00001$) (Fig. 2).

3.4 Association between SOD and T2DM

The meta-analysis of 8 included studies in this systematic review revealed a lower level of SOD in patients with T2DM compared to the controls, but the difference was not statistically significant [SMD (95% CI): -1.20 (-2.55, 0.15), $z = 1.75$, $p = 0.08$]. On the other hand, we observed a significant level of heterogeneity among the included studies for SOD ($I^2 = 98\%$, $p < 0.00001$) (Fig. 3-a).

3.5 Association between GSH and T2DM

Random-effects modeling of the meta-analysis revealed significantly lower levels of GSH in patients group compared to the control subjects [SMD (95% CI): -1.76 (-2.94, -0.59), $z = 2.94$, $p = 0.003$] with significant heterogeneity ($I^2 = 97\%$, $p < 0.00001$) (Fig. 3-b).

3.6 Association between GPX and T2DM

We found 4 papers that reported the GPX activity in diabetic patients. The meta-analysis revealed that there was no significant difference observed in the level of GPX in patients group when compared with that in control group [SMD (95% CI): 0.07 (-2.80, 2.94), $z = 0.05$, $p = 0.96$] (Fig. 3-c).

3.7 Association between TAS and T2DM

The meta-analysis of 5 including studies reported on TAS activity revealed that TAS level was significantly lowered in the patients group compared to the control group [SMD (95% CI): -1.40 (-2.28, -0.51), $z = 3.08$, $p = 0.002$] with the level of high heterogeneity ($I^2 = 96\%$, $p < 0.00001$) (Fig. 3-d).

3.8 Association between NO and T2DM

Based on a random-effects meta-analysis, comparing the NO level between the patient group and the control group, a significant difference was obtained for NO levels with a higher level in patients [SMD (95% CI): 1.40 (0.00, 2.81), $z = 1.95$, $p = 0.05$]. We observed a significant level of heterogeneity for NO level among the existing studies ($I^2 = 97\%$, $p < 0.00001$) (Fig. 3-e).

3.9 Publication bias

A funnel plot was used to analyze the publication bias in this systematic review and meta-analysis. The visual inspection of funnel plots of oxidative stress biomarkers in DM did not suggest potential publication bias except for GPX (Supplementary Fig. 1).

4. Discussion

Many studies have reported that OS is involved in the pathogenesis of multiple disorders including type 1 and type 2 diabetes [1,4]. To our best knowledge, this is the first systematic review and meta-analysis to find out the evidence on the association of OS biomarkers such as MDA, SOD, GSH, GPX, TAS, and NO levels in patients with T2DM. From our meta-analysis, we found significantly

higher levels of MDA and NO (considered as oxidants), and significantly lower levels of GSH and TAS (known as antioxidants) in patients compared to control subjects. On the other hand, we observed there was no significant difference in the levels of SOD and GPX between patients and control subjects. The overall results revealed that the impaired oxidants and antioxidants balance plays a vital role in the pathogenesis of T2DM.

In this meta-analysis, we observed a significantly increased level of MDA in patients with T2DM in almost all studies. Both experimental and clinical studies revealed that free radicals are formed in T2DM by glucose degradation, non-enzymatic glycation of proteins, and subsequent oxidative degradation [36–38]. The increased levels of free radicals may lead to lipid peroxidation and the level of MDA is usually measured as a well-known marker of lipid peroxidation [39]. As a marker of oxidants, the level of NO in diabetic patients was reported in this study, and the analysis revealed a higher level in patients compared to that of control groups.

It has been reported that the increase in lipid peroxidation is strongly associated with a decline in enzymatic and nonenzymatic antioxidant defense mechanisms [40]. This meta-analysis revealed that the levels of TAS and GSH were significantly lower in diabetic patients compared with those in control subjects. Although there was no association found in SOD and GPX with T2DM in this study. The included studies regarding the association of SOD and GPX levels with T2DM are limited and further studies with a larger sample size should be conducted to confirm the true association. The consequences of this imbalance between oxidants and antioxidants *i.e.* OS in T2DM can promote the development of complications in patients. A previous study reported that a decreased level of GSH can contribute to b-cell dysfunction and be involved in the pathogenesis of long-term complications of diabetes [41].

Some studies advocated that dietary supplementation of antioxidants like GSH precursor amino acid and antidiabetic drugs like gliclazide and metformin help scavenge the free radicals and reduce oxidative damage in the face of persistent hyperglycemia [33,42,43]. The role of gliclazide and metformin to increase the antioxidant capacity of erythrocyte catalase, GPX, and glutathione S-transferase enzyme in treated patients and reduced the OS in diabetes.

Although our study followed a standard search strategy in the current meta-analysis, this study has some limitations. The major limitation is observed in this study significant heterogeneity of the included studies, it might be due to the different measures and units was employed for the analysis of oxidative stress biomarkers in the included studies. Secondly, we did not analyze any correlation between the complications of T2DM with oxidative stress biomarkers due to inadequate data. Finally, subgroup analysis and meta-regression could not be performed in this meta-analysis due to the limited studies in the literature.

5. Conclusion

This systematic review and meta-analysis provide evidence that the increased OS has a major role in the pathogenesis and progression of T2DM. Therefore, further studies are needed to strengthen this evidence, especially on the association of SOD and GPX levels with T2DM.

Declarations

Research funding: This study didn't receive any specific grant from any organizations like the public or commercial.

Competing interests: We have declared that we have no competing interests.

Availability of data and material: Not applicable.

Code availability: Not applicable.

Ethical approval: Not required.

Informed Consent: No informed consent was necessary.

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Tables

Table 1: Characteristics of the included studies

Study, year	Country	Patients group				Control group				Evaluated parameters
		Number	Male	Female	Mean age (years)	Number	Male	Female	Mean age (years)	
Gallou <i>et al.</i> , 1993	France	60	40	20	55	53	24	29	35	Plasma-MDA
Sundaram <i>et al.</i> , 1996	India	200	NA	NA	49	180	NA	NA	50	Plasma-MDA, SOD, GPX, GSH
Vessby <i>et al.</i> , 2002	Sweden	38	14	24	32	41	22	19	30	Plasma-MDA
Bhatia <i>et al.</i> , 2003	India	30	12	18	46.9	30	11	19	46.3	Serum-MDA, NO Erythrocyte-SOD, GSH
Susleyici <i>et al.</i> , 2003	Turkey	107	52	55	57.8	99	46	53	55.5	Plasma-MDA, TAS
Memisogullari <i>et al.</i> , 2003	Turkey	38	21	17	53.1	18	10	8	49.3	Erythrocyte-SOD, GSH, GPX
Atli <i>et al.</i> , 2004	Turkey	19	9	10	70	15	6	9	72.2	Plasma-MDA Erythrocyte-SOD, GSH
Mahboob <i>et al.</i> , 2005	India	70	44	26	53	59	33	26	51.5	Serum-MDA, GSH
Gupta <i>et al.</i> , 2006	India	40	NA	NA	40	50	NA	NA	46	Serum-MDA, SOD, GPX
Song <i>et al.</i> , 2007	China	113	64	51	52.4	92	48	44	50.1	Plasma-MDA, TAS Erythrocyte-SOD, GSH
Kamal <i>et al.</i> , 2009	Egypt	50	29	21	NA	15	10	5	NA	Serum-MDA
Tangvarasittichai <i>et al.</i> , 2009	Thailand	50	12	38	68.9	40	14	26	65.5	Serum-MDA
Salem <i>et al.</i> , 2010	Egypt	50	27	23	NA	15	8	7	NA	Serum-MDA
Mallick <i>et al.</i> , 2011	India	50	27	23	50	30	16	14	52	Serum-MDA
Khemka <i>et al.</i> , 2014	India	102	54	48	51.5	95	49	46	53.1	Serum-MDA
Kumari <i>et al.</i> , 2014	India	50	25	25	48	50	25	25	48	Serum-MDA
Rani <i>et al.</i> , 2014	India	93	48	45	NA	93	48	45	NA	Serum-MDA, TAS
Shang <i>et al.</i> , 2015	China	28	NA	NA	29	40	NA	NA	29	Plasma-MDA, LPO,

										SOD, GPX, TAS
Al-Rawi <i>et al.</i> , 2015	UAE	25	NA	NA	50	25	NA	NA	54	Serum- MDA, SOD, GSH
Mishra <i>et al.</i> , 2017	India	92	59	23	52	51	20	31	47	Plasma- MDA, NO
Kulaksizoglu <i>et al.</i> , 2016	Turkey	35	20	15	65.74	35	21	14	67.6	Serum- MDA, NO, TAS
Banik <i>et al.</i> , 2018	Bangladesh	60	34	26	42.96	60	27	33	45.74	Serum- MDA, NO

MDA, Malondialdehyde; GSH, Glutathione; SOD, Superoxide dismutase; TAS, Total antioxidant status; GPX, Glutathione peroxidase; NO, Nitric oxide; CAT, Catalase

Table 2: Comparison of the level of MDA, SOD, GSH, GPX, CAT, TAS, and NO in patients and control group

Study, year	Patients group			Control group		
	Mean	SD	Number	Mean	SD	Number
MDA (mmol/L)						
Gallou <i>et al.</i> , 1993	3.11	0.43	60	2.84	0.28	53
Sundaram <i>et al.</i> , 1996	3.12	0.30	200	1.87	0.30	180
Vessby <i>et al.</i> , 2002	0.49	0.12	38	0.49	0.18	41
Bhatia <i>et al.</i> , 2003	4.1	0.11	30	2.89	0.25	30
Susleyici <i>et al.</i> , 2003	0.45	0.21	107	0.36	0.15	99
Atli <i>et al.</i> , 2004	0.33	0.7	19	0.31	0.06	15
Mahboob <i>et al.</i> , 2005	0.26	0.03	70	0.09	0.01	59
Gupta <i>et al.</i> , 2006	1.72	0.27	40	0.92	0.24	50
Song <i>et al.</i> , 2007	19.13	7.71	113	10.77	5.59	92
Kamal <i>et al.</i> , 2009	10.50	3.45	50	5.81	2.38	15
Tangvarasittichai <i>et al.</i> , 2009	2.75	0.15	50	1.65	0.12	40
Salem <i>et al.</i> , 2010	10.58	3.81	50	5.81	2.39	15
Mallick <i>et al.</i> , 2011	7.83	3.26	50	3.70	1.19	30
Khemka <i>et al.</i> , 2014	3.21	1.84	102	2.05	0.99	95
Kumari <i>et al.</i> , 2014	4.54	0.78	50	2.31	0.61	50
Rani <i>et al.</i> , 2014	3.61	0.63	93	1.93	1.51	93
Shang <i>et al.</i> , 2015	6.85	0.71	28	4.75	0.62	40
Al-Rawi <i>et al.</i> , 2015	2.38	0.97	25	1.12	0.35	25
Mishra <i>et al.</i> , 2017	2.47	0.53	92	1.43	0.23	51
Kulaksizoglu <i>et al.</i> , 2016	9.51	2.82	35	10.75	2.57	35
Banik <i>et al.</i> , 2018	5.38	1.64	60	2.63	1.63	60
SOD (U/mg Hb)						
Sundaram <i>et al.</i> , 1996	2.6	0.3	200	3.3	0.3	180
Bhatia <i>et al.</i> , 2003	0.54	0.09	30	1.04	0.12	30
Memisogullari <i>et al.</i> , 2003	2.2	0.6	38	2.5	1.0	18
Atli <i>et al.</i> , 2004	28.7	6.4	19	29.5	5.7	15
Gupta <i>et al.</i> , 2006	5.35	0.36	40	6.83	0.7	50
Song <i>et al.</i> , 2007	36.86	8.16	113	30.54	7.39	92
Shang <i>et al.</i> , 2015	72.27	18.81	28	117.06	15.63	40
Al-Rawi <i>et al.</i> , 2015	1.48	0.18	25	1.09	0.18	25
GSH (μmol/L)						
Sundaram <i>et al.</i> , 1996	48.1	7.5	200	54.0	3.1	180
Bhatia <i>et al.</i> , 2003	2.79	1.34	30	3.11	0.88	30
Memisogullari <i>et al.</i> , 2003	7.9	2.8	38	10.3	2.9	18

Atli <i>et al.</i> , 2004	7.1	1.7	19	8.8	2.4	15
Mahboob <i>et al.</i> , 2005	194.8	11.2	70	272.6	12.0	59
Al-Rawi <i>et al.</i> , 2015	2.15	0.87	25	3.22	0.70	25
GPX (U/mg Hb)						
Sundaram <i>et al.</i> , 1996	7.2	0.4	200	5.7	0.4	180
Memisogullari <i>et al.</i> , 2003	36.2	7.9	38	45.3	10.4	18
Gupta <i>et al.</i> , 2006	13.37	0.33	40	14.64	1.43	50
Shang <i>et al.</i> , 2015	7.75	1.29	28	10.84	2.84	40
TAS (μmol/L)						
Susleyici <i>et al.</i> , 2003	1.43	0.21	107	1.40	0.13	99
Song <i>et al.</i> , 2007	11.07	4.42	113	15.08	3.31	92
Rani <i>et al.</i> , 2014	0.46	0.46	93	1.69	1.34	93
Shang <i>et al.</i> , 2015	6.30	1.00	28	10.56	1.82	40
Kulaksizoglu <i>et al.</i> , 2016	1.15	0.16	35	1.48	0.11	35
NO (μmol/L)						
Bhatia <i>et al.</i> , 2003	50.2	36.2	30	36.7	7.40	30
Mishra <i>et al.</i> , 2017	12.76	1.43	92	7.44	1.26	51
Kulaksizoglu <i>et al.</i> , 2016	19.43	8.75	35	13.89	7.71	35
Banik <i>et al.</i> , 2018	47.20	70.88	60	15.86	14.95	60

MDA, Malondialdehyde; GSH, Glutathione; SOD, Superoxide dismutase; TAS, Total antioxidant status; GPX, Glutathione peroxidase; NO, Nitric oxide

Figures

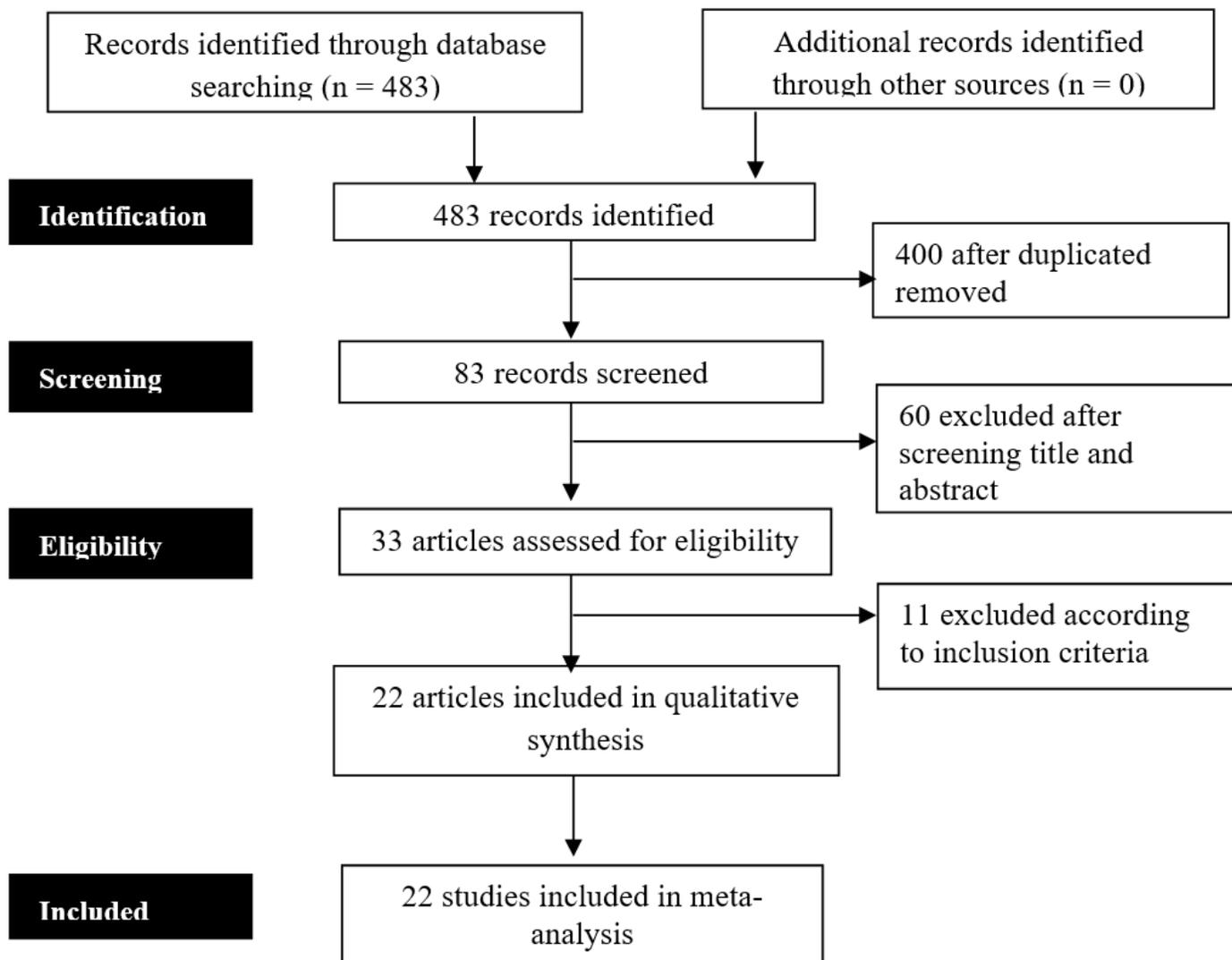


Figure 1

The flow diagram of the literature search and study selection according to PRISMA guidelines.

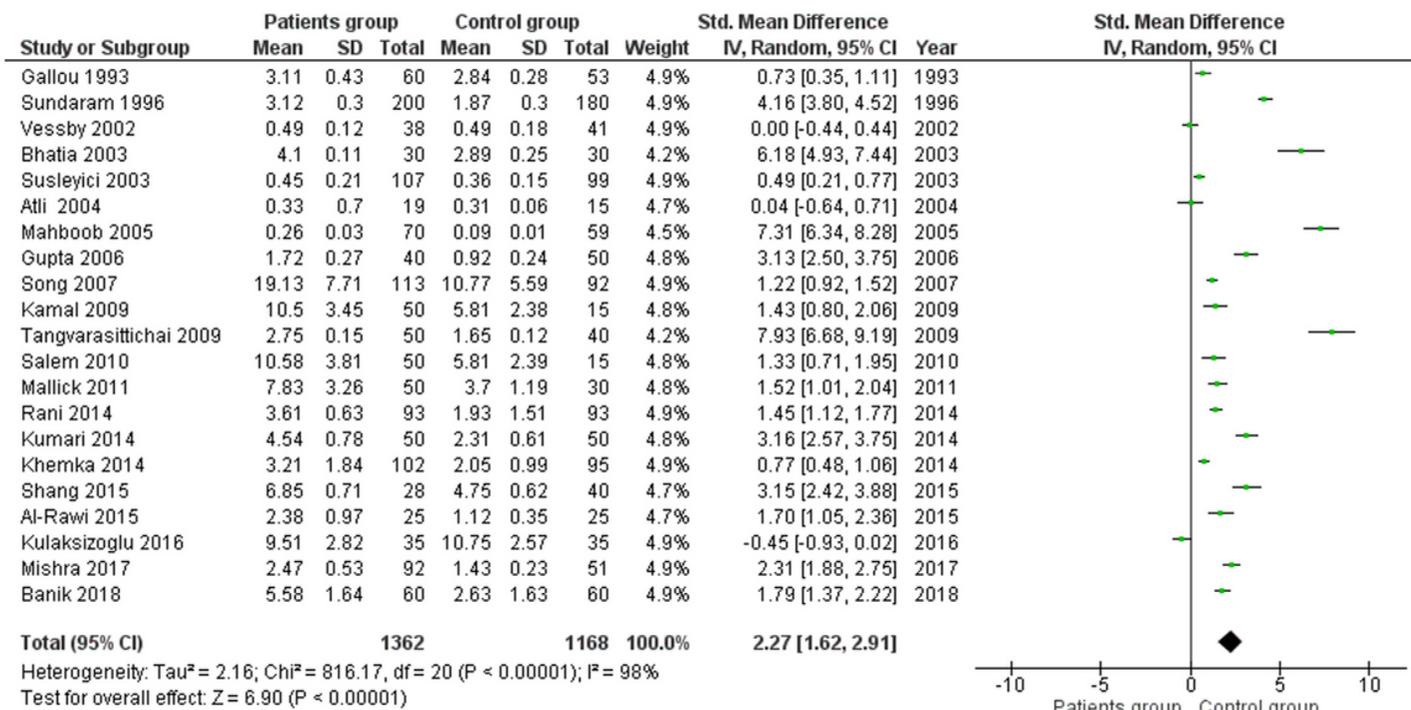
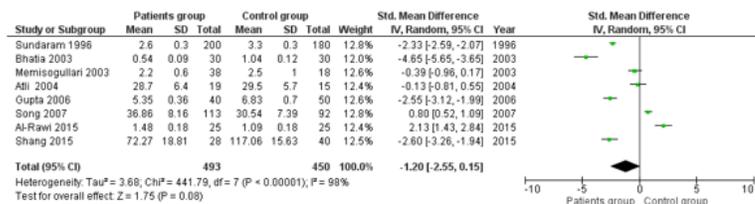


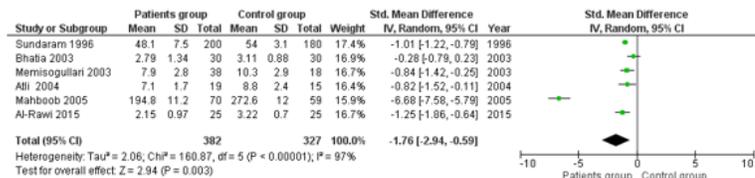
Figure 2

Forest plot of the random effects in a meta-analysis, showing the association of malondialdehyde with diabetes. Square denotes an effect estimate of individual studies with 95% Confidence Interval (CI) with the size of squares related to the weight assigned to the study in the meta-analysis.

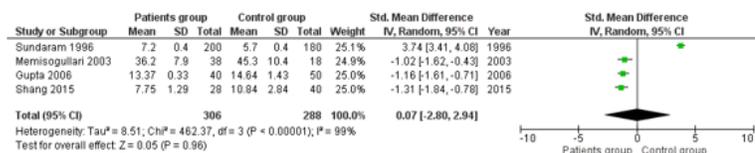
(a) Superoxide dismutase



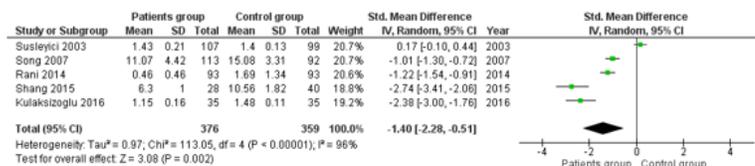
(b) Glutathione



(c) Glutathione peroxidase



(d) Total antioxidant status



(e) Nitric oxide

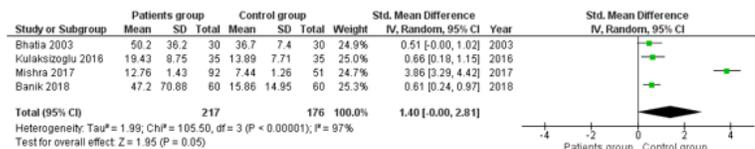


Figure 3

Forest plot of the random effects in a meta-analysis, showing the association of (a) superoxide dismutase, (b) glutathione, (c) glutathione peroxidase, (d) total antioxidant status, and (e) nitric oxide with diabetes. Square denotes an effect estimate of individual studies with 95% Confidence Interval (CI) with the size of squares related to the weight assigned to the study in the meta-analysis.

Supplementary Files

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- [SupplementaryFigure.docx](#)