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REVIEW ARTICLE

Dietary antioxidative supplements and diabetic retinopathy; a systematic review

Ozra Tabatabaei-Malazy[1,2] · Edris Ardeshirlarijani[3] · Nazli Namazi[4] · Shekoufeh Nikfar[2,5,6,7] · Reza Baradar Jalili[8] · Bagher Larijani[2]

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Abstract

Purpose There is controversial data regarding the effects of dietary antioxidative supplements on diabetic retinopathy (DR). We conducted a systematic review of both observational and randomized controlled clinical trials (RCTs) to clarify whether they are effective or not.

Methods All observational and RCTs conducted by antioxidative supplements on DR published up to 1 January 2018 in PubMed, Web of Sciences, Scopus and Cochrane Library databases were included. Exclusion criteria were animal studies, and studies conducted in Type 1 diabetes mellitus (T1DM), children or pregnant women. Main outcome measures were reporting the incidence or progression of DR in T2DM by assessment of visual fields, and measurements of oxidative and antioxidative biomarkers. The quality of reporting of included articles and risk of bias were assessed.

Results Finally, we reached 14 observational studies and 7 RCTs that conducted on 256,259 subjects. Due to severe methodological heterogeneity, only qualitative synthesis was carried. All studies were reported a significantly lower level of antioxidants and higher level of oxidative stress biomarkers in DR compared with others. There was an inverse significant correlation between vitamin C and malondialdehyde (MDA) ($r = -0.81$) or DNA damage ($r = -0.41$). These figures were statistically significant between vitamin E and MDA ($r = 0.77$) or superoxide dismutase ($r = 0.44$). Coefficient of correlation between MDA and zinc (−0.82), coenzyme Q10 (0.56), and magnesium (−0.73) was significant. Multi-oxidants trials were shown non-significant beneficial effects on DR.

Conclusions Although our study supports the positive effects of antioxidative supplements on DR, more high quality studies are needed to confirm.

Keywords Type 2 diabetes mellitus · Diabetic retinopathy · Oxidative stress · Antioxidants

The original article has been corrected.

Ozra Tabatabaei-Malazy and Edris Ardeshirlarijani equally contributed as first author.

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✉ Bagher Larijani
emrc@tums.ac.ir

Ozra Tabatabaei-Malazy
tabatabaeiml@sina.tums.ac.ir

Edris Ardeshirlarijani
ediardeshir@gmail.com

Nazli Namazi
nazli.namazi@yahoo.com

Shekoufeh Nikfar
shekoufeh.nikfar@gmail.com

Reza Baradar Jalili
reza.jalili@ubc.ca

Extended author information available on the last page of the article

Abbreviations

NPDR	Non-proliferative diabetic retinopathy
PDR	Proliferative diabetic retinopathy
DR	Diabetic retinopathy
IDF	International Diabetes Federation
PKC	Protein kinase C
AGEs	Advanced glycation end products
ROS	Reactive oxygen species
Mg	Magnesium
Zn	Zinc
MDA	Malondialdehyde
B1	Benfotiamine
ALA	Alpha lipoic acid
Se	Selenium
T2DM	Type 2 diabetes mellitus
RCTs	Randomized controlled trials
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
GPx	Glutathione peroxidase
SOD	Superoxide dismutase
TAS	Total antioxidant status
STROBE	Strengthening the reporting of observational studies in epidemiology
ADA	American Diabetes Association
VC	Vitamin C
VE	Vitamin E
VD	Vitamin D
BCVA	Best-corrected visual acuity
IOP	Intraocular pressure
RNFL	Retinal nerve fiber layer thickness
FORT	Free oxygen radical test
CMT	Central macular thickness
NF-κB	Nuclear translocation factor- κB
VEGF	Vascular endothelial growth factor
BAP	Biological antioxidant potential
OP	Oscillatory potential
Cu	Copper
Mn	Manganese

Introduction

Diabetic retinopathy (DR) that is definded as retinal micro-vascular lesion in subjects with diabetes classified as non-proliferative (NPDR) and proliferative diabetic retinopathy (PDR). NPDR can increase the risk for development of PDR and blindness. The prevalence of diabetic retinopathy (DR) as a common microvascular complication of diabetes is increasing worldwide. DR as the leading cause of vision loss in working-age adults affects 35% of patients with diabetes [1]. Based on report of International Diabetes Federation (IDF) there are approximately 425 million patients with diabetes in 2017 that expects to rise to 629 million by 2045. Studies in various countries have revealed an increasing trend in economic burden of DR [1, 2]. However, blindness due to DR can be prevented by appropriate screening and treatment. IDF is reported 76% reduction in the onset of DR through intensive control of hyperglycemia [1].

Within several pathways that have linked hyperglycemia to DR, oxidative stress has a crucial role in the pathogenesis of DR [3]. Oxidative stress is defined as a condition with an imbalance between oxidants and antioxidant defense system of the body [4]. This condition can be modified by enzymatic and non-enzymatic antioxidants [5–7]. Hyperglycemia-induced metabolic abnormalities including activation of polyol pathway, protein kinase C (PKC), advanced glycation end products (AGEs), and hexosamine pathway besides inflammatory mediators could increase production of reactive oxygen species (ROS) and oxidative stress that resulted in dysfunction of mitochondria, apoptosis and diabetic retinopathy [8]. Although circulating high glucose is the main investigator of DR development, other factors such as duration of diabetes, dyslipidemia and hypertension are also influenced on progression of DR [8].

Due to a potential association between diabetes' complications and oxidative stress, it is logical to expect beneficial effects for antioxidants in improvement diabetes and its complications. The retina is disposed to damage by oxidative stress due to its polyunsaturated fatty acids-rich tissue, highest oxygen uptake than any tissue and high vascularization [9]. Although majority of the antioxidants can be consumed easily from foods, their effects on DR have been seen by influencing on one or more complex mechanisms [7]. Evidences have shown that DR can be controlled and prevented by several antioxidant supplements including vitamins C, E, D, beta-carotene, co-enzyme Q10, magnesium (Mg) and zinc (Zn) via the reduction of protein glycosylation, inhibition of LDL-oxidized formation; malondialdehyde (MDA), anti-inflammatory effects, or protection of insulin in release, production, and secretion [10–13]. Beneficial effects of antioxidants have shown in animal models of DR, but clinical trials have provided controversial results [14]. In this systematic review, we aimed to critically assess the effect of supplementations with antioxidants vitamins A, C, D, E, benfotiamine (B1), beta-carotene, alpha lipoic acid (ALA), co-enzyme Q10, selenium (Se), Mg, and Zn on DR in patients with type 2 diabetes mellitus (T2DM) based on current relevant data from both observational and randomized controlled trials (RCTs) conducted studies.

Methods

Data searches

All relevant available observational studies including cohort, case-control, and cross sectional studies as well as RCTs which reported the effects of antioxidative supplements,

vitamins A, C, D, E, B1, ALA, beta-carotene, co-enzyme Q10, Se, Mg and Zn on diabetic retinopathy and published up to 1 January 2018 were included. To obtain all related studies, PubMed, Cochrane Library, Web of Science, and Scopus web databases were searched using search strategy referred in Supplementary 1.

In order to obtain required information, we sent maximum 3 e-mails to the corresponding authors of publications with insufficient data. According to PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) flowchart [15] the title and abstract of publications were examined after exclusion of duplicated articles. Finally, reference list of potentially eligible studies were assessed by hand searching for full-text retrieval. All steps were performed independently by two investigators. Any disagreement was resolved by the third reviewer.

Study selection

All observational studies or RCTs that reported the incidence or progression of DR in subjects with T2DM were included. All diagnostic methods such as visual fields' assessment, by ophthalmoscopy, fluor-angiography, electro-retinography, visual acuity, beside measurements of oxidative biomarkers; MDA, and antioxidative biomarkers such as glutathione peroxidase (GPx), superoxide dismutase (SOD), and total antioxidant status (TAS) were acceptable.

Exclusion criteria were as following; (i) animal studies, (ii) studies on healthy population, type 1 DM, children and pregnant women. Review articles, letters to the editor, conference abstract, interview and thesis were also excluded. English language was considered to restriction of search.

Data extraction and quality assessment

The following data were extracted; first author, year of publication, study design, age and sex of participants, sample size, number of participants and patients with T2DM in observational studies, frequency and dosage of dietary supplement, duration of intervention, follow up, serum level of dietary supplement, outcome measures, and significant results.

The authors independently assessed the quality of all included observational and RCTs by STROBE (strengthening the reporting of observational studies in epidemiology) and Jadad scoring system [16, 17], respectively. Any disagreement was resolved by discussion and if not to reach consensus, third investigator solved the problem.

Five selected items from the recommended checklist of STROBE was used for quality assessment. The items included a) 1 point if confirmed diagnosis of diabetes based on accepted criteria such as American Diabetes Association (ADA), or medical records; (b) 1 point if provided inclusion and exclusion criteria; (c) 1 point if presented key elements of study design; d) 1 point if assessed taking of dietary supplements by a valid questionnaire, tool, or laboratory measurements; and (e) 1 point if described characteristics of participants. The range of score in the Jadad scale was between 0 and 5. The quality score lower than 3 points in both of observational studies and RCTs were classified as low quality or high risk of bias studies. Considerable heterogeneity among studies did not allow us to perform meta-analysis.

Results

According to the PRISMA flowchart (Fig. 1), 21 articles are included in the present systematic review [10–12, 18–35]. Characteristics of the included observational studies and RCTs are shown in Table 1, and Table 2, respectively.

Studies' characteristics

All included studies were conducted in adult patients; 256,727 subjects. Among them, 14 studies [10–12, 18–28] were observational studies involving 163,913 participants with diabetes (163,445 with T2DM) and the remaining 7 articles were RCTs [29–35] with 92,814 total subjects with diabetes and 92,784 patients with T2DM. All of the studies were performed on adults aged 20–80 years in both genders. Most of the observational studies and RCTs were conducted to evaluate the effect of vitamins C or E on DR [10, 12, 18–20, 22, 24–28, 30–35]. It was not found any observational studies or RCTs to evaluate the effect of vitamin A on DR. Details of the included studies are described as below.

Association between dietary antioxidative supplements and DR in observational studies

Vitamin C

All 10 observational studies reported lower vitamin C (VC) levels in subjects with DR compared to those without DR [10, 12, 18–20, 22, 24, 25, 27, 28]. Gupta et al. [20] found a significant acceleration in oxidative stress biomarkers and a reduction in VC level with DR progression. Kumari et al., and Lam et al., reported an inverse significant correlation between malondialdehyde (MDA) and DNA damage; as oxidative stress biomarkers and VC that equaled −0.81, and − 0.41, respectively [10, 24].

Vitamin E

All 6 observational studies that assessed vitamin E (VE) level showed a significant lower serum level in subjects with DR than others [10, 12, 24–26, 28]. Kumari et al., and Lam et al. [10, 24] found positive significant associations between MDA

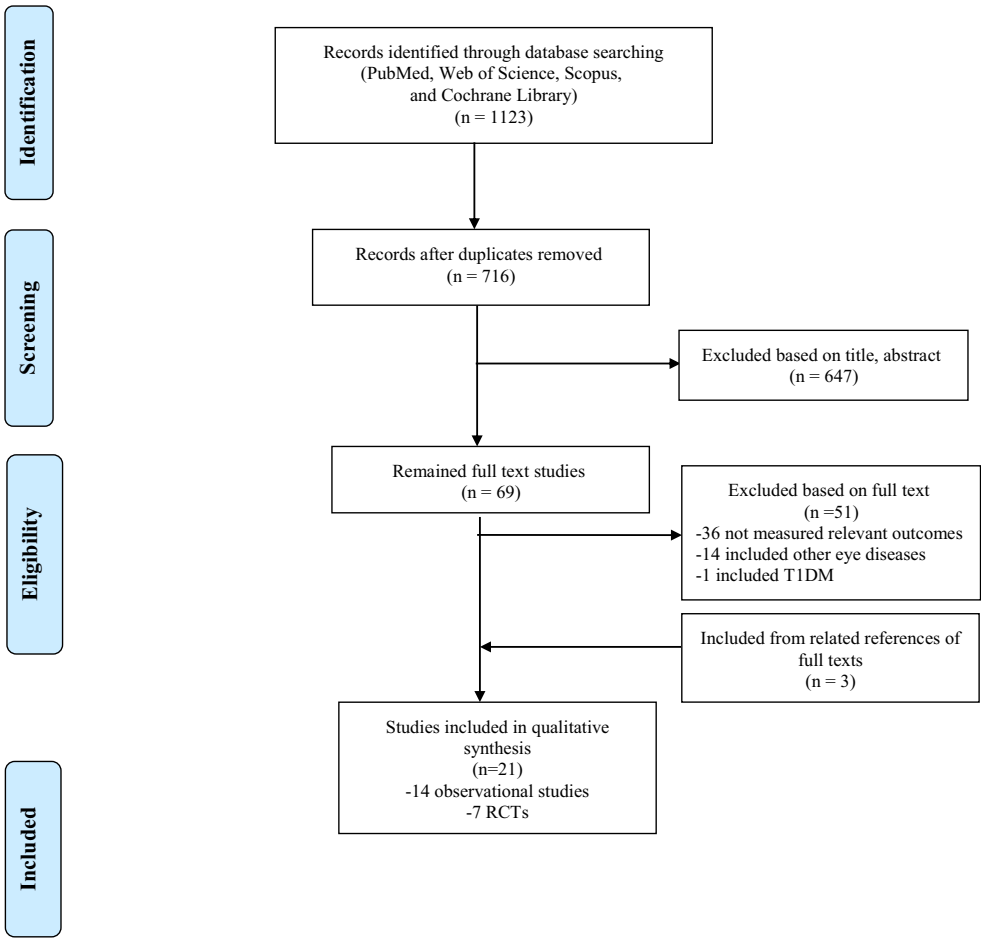

Fig. 1 Flow diagram of the study selection process

and allantoin as oxidative stress biomarkers and VE; r = 0.77, and 0.33, respectively. Said et al. [26] reported a significant lower level of SOD and GPx in DR with greater reduction in proliferative DR. In addition, they found significant positive correlations between SOD/GPx with VE; r = 0.44, and 0.34, respectively.

Other antioxidative dietary supplements

In one observational study that assessed the correlation between vitamin D (VD) and DR [28] lower level of vitamin in patients with DR than other participants was reported. Three studies showed lower levels of Zn in patients with DR compared to those without DR [12, 23, 28] and one study showed no significant differences in the serum levels of Zn between patients with proliferative DR and non-proliferative DR [21]. Kumari et al. [12] revealed a significant inverse correlation between MDA and Zn (r = −0.82). Just in one study was reported the lower level of coenzyme Q10 in DR than others [11]. They also found a significant positive correlation between MDA and coenzyme Q10 (r = 0.56). Researchers of two studies [12, 28] found lowest level of Mg in DR versus others. In addition, it was reported an inverse significant association between MDA and Mg (r = −0.73) [12]. In one study was observed lower serum level of Se in T2DM especially in patients without DR than control group [28].

Association between dietary antioxidative supplements and DR in RCTs

All of RCTs were used mixture of antioxidants except Chatziralli et al. [35] that supplemented VE for patients with DR. In most RCTs, VE was recommended in combination with VC [30, 31, 33, 34]. Intake of vitamins C and E concomitant other antioxidative supplements for 18 months follow up was shown non-significant effect on best-corrected visual acuity (BCVA), intraocular pressure (IOP), and retinal nerve fiber layer thickness (RNFL) [33]. Sole intake of 300 mg VE for 3 months could significantly decrease serum level of MDA that was associated with significant good response to VE in those had PDR without prior laser therapy [35]. In one study, an improvement of visual acuity, and foveal thickness with mixture of lutein and zeaxanthin was observed [29]. Dosage of lutein in this trial was 6 mg with a follow-up duration of 3 months. Intake of 3 mg lutein mixed with other antioxidants including VC, alpha-tocopherol, niacin, beta-carotene, Zn, and Se for 60 months [30] was not showed any significant

Table 1 Data extracted from eligible observational studies in qualitative systematic review

Study	Design	Subjects	Sex/age years	Outcome measures	Significant Results/Odds Ratios	Quality score
Sinclair et al. 1992 [18]	Cross-sectional	Total 90 (40 healthy, 25 T2DM with DR, 25 T2DM without DR)	Both/> 60	Fundoscopy, measurements of TBA reactivity, GSH, AA, DHA, TGs, TChol, glucose, fructosamine	-↓AA in DR vs. Others ($P < 0.01$) -↑DHA/AA in DR vs. Without DR ($P < 0.001$), or controls ($P < 0.0001$) -Negative correlation between AA and fructosamine in DR ($r = -0.46$, $P < 0.05$)	2
Gurler et al. 2000 [19]	Case-control	Total 85 (26 healthy, 34 T2DM, 25 T2DM + DR)	Both/42–69	MDA-like metabolite, erythrocyte GPx, SOD, VC, HbA1C	-↓VC in T2DM + DR -↑MDA-like metabolite in T2DM + DR -↑HbA1C in T2DM with/without DR	3
Gupta et al. 2005 [20]	Case-control	Total 132 (50 healthy, 40 T2DM without DR, 42 T2DM+ DR)	Both/38–54	MDA, SOD, GPx, VC, BG, HbA1C	-↓Serum level VC in T2DM with/without DR vs. healthy -↑Serum level MDA, SOD, GPx in T2DM with/without DR vs. Healthy -↓SOD, VC with DR progression -Positive correlation between MDA, HbA1C and duration of DR	4
Yildirm et al. 2007 [21]	Case-control	Total 75 (25 non-T2DM, 25 T2DM+ DR proliferative, 25 T2DM + DR non-proliferative)	Both/50–77	HbA1C, serum Cu, Zn, NO, GSH, AOPP level, SOD	-↑AOPP in T2DM Proliferative -↑NO, Cu in T2DM vs. Non-T2DM -↓GSH in T2DM vs. Non-T2DM -↑HbA1C in T2DM vs. Non-T2DM	2
Kumari et al. 2008 [10]	Case-control	Total 118 (32 healthy, 36 T2DM, 50 T2DM + DR)	Both/48–68	MDA, VE, VC, lipid profile, FBS, 2hppBS	-↑MDA in T2DM with/without DR -↓VE, VC in T2DM especially T2DM+ DR -Positive correlation betwen MDA/VE ($r = 0.77$) -Negative correlation between MDA/VC ($r = -0.81$) -Positive correlation between MDA/FBS ($r = 0.81$) -Positive correlation between MDA/lipid profile except HDL-C	5
Samuel et al. 2010 [22]	Case-control	Total 90 (30 healthy, 30 T2DM, 30 T2DM+ DR)	Both/35–65	MDA, erythrocyte SOD, GSH, VC, FBS	-↑MDA in T2DM+ DR -↓SOD, GSH, VC in all T2DM especially T2DM + DR -Negative correlation between FBS and antioxidant enzymes in T2DM + DR	2
Aldebasi et al. 2011 [23]	Case-control	Total 160 (60 T2DM, 100 T2DM+ DR)	Both/ 61	FBS, HbA1C, MDA, 8-OhdG,Cu-Zn SOD	-↑MDA, 8-OhdG in T2DM+ DR vs. Others -↓Cu-Zn SOD in T2DM+ DR vs. Others -Negative correlation between MDA or HbA1C and Cu-Zn SOD ($r = -0.24$, $r = -0.23$)	4
Lam et al. 2011 [24]	Case-control	Total 420 T2DM (46 without DR, 161 background DR, 207 non-PDR, 6 PDR)	Both/ <75	FBS, lipid profile, HbA1C, DNA Damage, serum VC, SOD, TAS, GPx, VE lipid standardized, allantoin, urine level F2-isoprostanes	-Positive correlation between DNA damage and HbA1C ($r = 0.32$), and FBS ($r = 0.52$) -Negative correlation between DNA damage and VC ($r = -0.41$) -Negative correlation between DNA damage and TAS ($r = -0.21$) -Positive correlation between VE lipid standardized and allantoin ($r = 0.33$)	4
Ates et al., 2013 [11]	Case-control	Total 100	Both/50–70			4

Table 1 (continued)

Study	Design	Subjects	Sex/age years	Outcome measures	Significant Results/Odds Ratios	Quality score
		(50 healthy, 50 T2DM + DR proliferative)		Ubiquinone-10, total coenzyme Q10, ubiquinol-10/ ubiquinone-10, MDA	-Positive correlation between MDA and coenzyme Q10 (r = 0.557) -↑MDA in T2DM+ DR -↑Ubiquinone-10 in T2DM+ DR -↓Ubiquinol-10/ubiquinone-10 in T2DM+ DR	
Roopa et al. 2013 [25]	Case-control	Total 150 (50 healthy, 50 T2DM, 50 T2DM + DR)	Both/ NA	MDA, VC, VE, hs-CRP	-↑MDA and hs-CRP in T2DM with/without DR especially in DR -↓VC, VE in T2DM with/without DR especially in DR	3
Said et al. 2013 [26]	Case-control	Total 120 (30 healthy, 30 T2DM, 30 T2DM+ PDR, 30 T2DM+ non-PDR)	Both/40–70	FBS, lipid profile, SOD, GPx, VE	-↑Lipid profile (except HDL-C) in T2DM+ DR -↓SOD, GPx, VE in T2DM + DR especially proliferative -Positive correlation between GPx and VE (r = 0.34) -Positive correlation between SOD and VE (r = 0.44)	3
Kumari et al. 2014 [12]	Case-control	Total 112 (40 healthy, 30 T2DM, 42 T2DM + DR)	Both/50–70	FBS, Mg, Zn, VC, VE, MDA	-↓Mg, Zn in T2DM especially with DR -↑MDA in T2DM with/without DR -↓VC,VE in T2DM with/without DR -Negative correlation between MDA and Mg (r = −0.73), and Zn (r = −0.82)	3
Kundu et al. 2014 [27]	Case-control	Total 150 (50 healthy, 50 T2DM, 50 T2DM + DR)	Both/40–70	FBS, HbA1C, MDA, erythrocyte GSH, VC	-↑FBS, HbA1C, MDA, SBP in T2DM with/without DR -↓VC, erythrocyte GSH in T2DM with/without DR -Negative correlation between FBS and VC (r = −0.58) -Positive correlation between FBS and MDA (r = 0.47)	4
Longo-Mbenza et al. 2014 [28]	Case-control	Total 192 (45 healthy, 84 T2DM, 66 T2DM+ DR)	Both/37–70	8-isoprostane, 8-oHdG, serum GGT, antibody against OxLDL, TBARS, GSH, SOD, GPx, FBS, HOMA, TAS, Zn, Se, Mg, VC, VD, VE, ApoB, eye examination, visual acuity, Lipid profile	-↑Lipid profile in T2DM vs. healthy -Highest oxidant markers and lowest antioxidants in T2DM+ DR vs. others -↑HOMA in T2DM vs. healthy	5

T2DM Type 2 diabetes mellitus, *DR* Diabetic retinopathy, *MDA* Malondialdehyde, *SOD* Superoxide dismutase, *GPx* Glutathione peroxidase, *VC*, Vitamin C; *BG* Blood glucose, *HbA1C* Glycosylated hemoglobin, *vs.* versus, *GSH* Reduced glutathione, *FBS* Fasting blood sugar, *VE* Vitamin E, *2hppBS* 2 h post prandial blood sugar, *HDL-C* High density lipoprotein cholesterol, *8-oHdG* 8-hydroxydexoxyguanosine, *GGT* Gamma-glutamyltransferase, *OxLDL* Oxidized low density lipoprotein, *TAS* Total antioxidant status, *Mg* Magnesium, *VD* Vitamin D, *ApoB* Apolipoprotein B, *TBARS* Thiobarbituric acid reacting substances, *HOMA* Hemostasis model-based insulin resistance, *NO* Nitric oxide, *AOPP* Advanced oxidation protein products, *Zn* Zinc, *Cu* Copper, *Se* Selenium, *SBP* Systolic blood pressure, *NA* Non access, *Hs-CRP* High sensitivity c-reactive protein, *AA* Ascorbic acid, *DHA* Dehydroascorbic acid, *TChol* Total cholesterol, *PDR* Proliferative diabetic retinopathy

Table 2 Data extracted from eligible RCTs in qualitative systematic review

Study	Design	Subjects/ sample size	Age (yr)	Sex	Supplement	Duration (month)	Dosage	Indicator	Main results	Quality Score
Bo-Jie Hu et al. 2011 [29]	Quasi-Experimental	Total 90 (30 healthy, 30 non-PDR with treatment, 30 non-PDR non-treatment)	59	M/F	lutein + zeaxanthin	3	6 mg + 0.5 mg	BCVA, CS, OCT	After medication: -Improvement of VA -↑Sig CS -↓Sig Foveal thickness	3
Garcia-Medina et al. 2011 [30]	RCT	Total 105 (62 T2DM with non-PDR with treatment, 43 T2DM with non-PDR without treatment)	30–65	M/F	Mixture: VC, Alpha-Tocopherol Niacin b-Carotene Lutein, Zn Cu Se Manganese Proteins CH Fat	60	2tablets/day 60 mg 10 mg 10 mg 3 mg 3 mg 13.5 mg 1 mg 10 mcg 1 mg 130 mg 60 mg 230 mg	MDA, TAS, aBCVA, DR score	-↓Sig MDA in both groups -↓Sig TAS in placebo and ↑NS in treatment group -NS change in aBCVA -↑Sig DR score in placebo and ↑NS in treatment group	3
Nebbioso et al. 2012 [31]	RCT	Total 32 (16 pre-DR in treatment, 16 pre-DR in placebo)	57	M/F	Mixure: ALA, genistein, VC,VE, B complex	1	400 + 80 + 30 + 5 + 15 mg	FORT, d-ROM BAP	-↑Sig. BAP by treatment -↑Sig. OP by treatment	3
Domanico et al. 2015 [32]	RCT	Total 68 (34 Non-PDR with/without supplements)	40–79	M/F	A mixture: Pycnogenol, Coenzyme Q10, VE	6	1 tablet/ day (50+ 20+ 30 mg)	CMT FORT	-↑NS BCVA in both groups -↓Sig. FORT at 3 mo, ↓NS at 6 mo treatment -↓Sig. CMT at 3 mo, ↓NS at 6 mo treatment -NS correlation between FORT and CMT	2
Roig Revert et al. 2015 [33]	RCT (Community-Based Study Design)	Total 208 (68T2DM with DR, 62 T2DM without DR, 78 healthy)	25–80	M/F	Mixture: DHA, vitamins E, C, B1, B2, B3, B6, B9, B12, lutein, zeaxanthin, glutathione, hydroxytyrosol, Se, Mn, Zn, Cu	18	Not clear	MDA, TAS, HbA1C, BS, lipid profile, BCVA, retinal thickness, IOP	At baseline: -↑Sig. Oxidative stress,inflammatory, vascular risk markers in T2DM + DR vs. others -↓Sig.TAS in T2DM + DR vs. others After treatment: -↓Sig MDA in T2DM+ DR -↑Sig TAS in T2DM + DR	2

Table 2 (continued)

Study	Design	Subjects/ sample size	Age (yr)	Sex	Supplement	Duration (month)	Dosage	Indicator	Main results	Quality Score
									-↑Sig HbA1C in T2DM + DR -NS changes in lipid profile in T2DM ± DR -↓NS BCVA -↓NS IOP in T2DM + DR -↑Sig IOP in T2DM-DR -↑Sig RNFL in T2DM ± DR -↑NS MT in T2DM+ DR -↓NS MT in T2DM- DR	
Rodríguez-Carrizalez et al. 2016 [34]	RCT	Total 60 (20 Non-PDR in each group)	60	M/F	Group 1: Coenzyme Q10 Group 2: Mixture of lutein, astaxanthin, zeaxanthin,VC,VE, Zn, Cu Group 3: placebo	6	400 mg 10 + 4 + 1 + 180 + 30 + 20 + 1 mg	HbA1c, FBS, Lipid profile, LPO, Nitrites/ Nitrates, TAC, CAT, GPX, CVA, LEP	-↓NS HbA1C, FBS, Tchol, LDL, TG by treatment -↑NS HDL by treatment -↓Sig. LPO, Nitrites/ Nitrates, CAT, GPx by treatment -↑Sig. TAC by treatment -NS change in CVA in all groups -NS decraese in LEP in all groups	2
Chatziralli et al. 2017 [35]	Quasi-experimental	Total 282 (282 Insulin-dependent T2DM + DR in different stages)	50–70	M/F	VE	3	300 mg	MDA, DR degree, HbA1C	-↓Sig. MDA in all DR stages -↑Sig response to VE in PDR by treatment naïve vs. prior laser photocoagulation	0

CMT Central macular thickness, *FORT* Free oxygen radical test, *MDA* Malondialdehyde, *TAS* Total antioxidant status, *aBCVA* Average best corrected visual acuity (average of both eyes of each patient on a decimal scale), *LPO* Lipo-peroxidation products, *NS* Non significant, *d-ROM* reactive oxygen metabolites, *BAP* Biological antioxidant potential, *OP* oscillatory potential, *CS* Contrast sensitivity, *OCT* optical coherence tomography, *PDR* proliferative diabetic retinopathy, *MT* Macular thickness, *IOP* Intraocular pressure, *RNFL* Retinal nerve fiber layer thickness, *CAT* Catalase, *TAC* total antioxidant capacity, *LEP* Left eye pressure, *CVA* Corrected visual acuity, *CH* Carbohydrate

changes in BCVA. Percentage of onset/ progression of DR in T2DM with DR were retarded from 61% to 39% and from 92% to 8%, respectively after 18 months follow up with/ without supplementation. These figures were worsened in those without DR from 9% to 91% and from 35% to 65%, respectively after 18 months follow up with/ without supplementation. Coenzyme Q10 was consumed with/without other antioxidative supplements in two studies [32, 34]. Treatment with mixture of 20 mg coenzyme Q10 and other antioxidants could be resulted in non-significant increase in BCVA and significant decrease in free oxygen radical test (FORT) and central macular thickness (CMT) after 6 months follow up [32]. Sole intake of 400 mg coenzyme Q10 could non-significantly improve level of HbA1C, lipid profile, visual acuity, and eye pressure, while could significantly improve level of oxidative and antioxidative biomarkers [34]. Mixture of ALA with other antioxidants including genistein and vitamins was shown a significant beneficial effect on antioxidant potential (BAP) test and electroretinogram oscillatory potential (OP) values [31].

Discussion

This systematic review of fourteen observational studies and seven RCTs demonstrated in patients with T2DM and DR was shown lower level of antioxidants parameters and higher concentrations of oxidative stress biomarkers than those without DR. Based on RCTs, it seemed taking mixture of antioxidative supplements can be helpful for DR.

In our included observational studies, serum level of VC and VE in patients with T2DM and DR was lower than those with healthy individuals. Some evidences showed that VC and VE can protect retina against DR through (i) scavenging of free radicals, (ii) decreasing production of ROS, (iii) suppression lipid peroxidation (or MDA formation), and (iv) reducing leukocyte adhesion in retinal vessels [3, 6, 7, 36–38]. Since, reported beneficial effects of mixed VC with VE in observational studies or trials may be related to intake of fruits and vegetables as a main source of mixture of micronutrients and existence possibility a synergism interaction between antioxidative supplements, it is reasonable to respond better to the mixture mode of dietary antioxidants than sole intake [39]. Therefore, it is supposed suitable type and appropriate dosage of supplements beside suitable selection in combination with each other can be helpful. The beneficial effects of combination of VC with VE have confirmed in several complications of diabetes [6, 40]. The mixture of VC and VE in diet of animal model of DR could be resulted in the reduction of retinal neovascularization by increasing antioxidant defense system and decreasing ROS levels [40]. However, administration of VC and VE with other antioxidants could be led to better response than sole intake of VC or VE due to prevent activation of PKC, and decrease production of nitric oxide and formation of micro-vascular lesions in the retina [40]. Our findings in three RCTs have shown similar effects [30–32]. Mixture of VC and VE with niacin, beta-carotene, lutein, zeaxanthin, ALA, B complex, genistein and some trace elements have demonstrated some vision protections that was significant in retinal thickness and non-significant in visual acuity in our included RCTs. It should be noted that not only total daily dosage of VC (30–180 mg) and VE (5–30 mg), but also duration of studies were inappropriate in our multi-antioxidants' mixture. Although in some studies, a single high dose of vitamins C and E was taken, high intake does not necessarily mean a full absorption [41]. It was established that development of many pathological changes in diabetes has occurred few years before their presentation in clinic. On the other word, it may need more than 5 years to reverse the pathological changes by antioxidative supplementation [42]. Therefore, it was not observed any significant changes in visual acuity after a few months.

Administration of ALA in diabetic rats has ameliorated activation of nuclear translocation factor κB (NF-κB), scavenging ROS, decreasing retinal level of vascular endothelial growth factor (VEGF), and protection of retina against ischemic injury [43, 44]. ALA can protect mitochondria against oxidative damage via prevention of mitochondrial dysfunction, apoptosis of capillary cell of retina, and development of DR in experimental study on rats [43]. In addition, ALA has beneficial effects on contrast sensitivity in type 1 and two diabetes mellitus [45]. In our study, administration of 400 mg ALA with other antioxidants including genistein, vitamins C, E and B complex was significantly increased Biological antioxidant potential (BAP) test and oscillatory potential (OP) values after treatment [31].

Lutein and zeaxanthin are both carotenoid with antioxidative properties. Lutein and zeaxanthin are most important carotenoids that exist in peripheral and fovea of retina, respectively. It was demonstrated a special effect for lutein and zeaxanthin on binding protein gene expression through enhancing synaptic connections of cells in nervous system. Thus, it resulted in increasing contrast sensitivity [46]. In addition, lutein and zeaxanthin can protect retina against neovascularization by decreasing permeability and leakage of vessels as well as prevention of combining free radicals with retinal collagen [47]. However, overdose of carotenoid supplementation could cause apoptotic cell death and should be used with caution [48]. In our study, combination of lutein with zeaxanthin and other antioxidants was improved visual acuity, foveal thickness, and contrast sensitivity in DR [29, 30, 32, 34]. Possible protecting mechanisms against oxidative stress by multi-antioxidants may related to synergistic interaction between vitamins C and E, carotenoids, and trace elements such as Se, Zn, copper (Cu), and manganese (Mn) in scavenging free radicals, and ameliorating the mitochondrial dysfunction [32, 44].

Coenzyme Q10 has a key role in oxidative phosphorylation of mitochondria by electron carrying [49]. Several studies were demonstrated its beneficial effects on endothelial function in patients with T2DM, cardiovascular diseases and animal model of diabetic nephropathy [50–52]. Coenzyme Q10 can reduce oxidative stress by recoupling endothelial nitric oxide synthase or through influence on respiratory chain of mitochondria. In two RCTs, 20 mg coenzyme Q10 combined with VE and pycnogenol or 400 mg sole intake was associated with a non-significant improvement in visual acuity and central macular thickness in patients with NPDR [33, 34].

There is lack of evidence on long-term safety of antioxidative nutrients on DR. Accordingly; it is better to increase intake of nutrients from natural food sources (8–10 servings of fruits and vegetables) according to American Diabetes Association recommendation [53].

Our study has some strengths and limitations. The most important strength of this study is that this study assessed critically all observational studies and RCTs on the effect of dietary antioxidative supplementation in patients with T2DM and it was the first systematic review in this topic. However, some potential limitations should be addressed. First, most of included studies had small sample size and participants consumed varied dosage of multi-antioxidants not sole intake that resulted in methodological heterogeneity. So, we could not perform meta-analysis. Second, the quality of included observational and RCTs in this study was varied. Out of twenty-one included studies, just eleven observational studies and three trials had high-quality.

Conclusion

This systematic review has attempted to offer antioxidative supplements as the target therapeutic agents for prevention or retarding the progression of DR. Antioxidants could effect on the development of DR by targeting multiple steps of oxidative stress and mitochondrial damage. Therefore, it is expected that supplementation with antioxidants may prevent DR in patients with T2DM. However, most evidences on beneficial effects of dietary antioxidative supplements have been encouraged by animal studies. Due to lack of well-designed and high quality longitudinal and RCTs, more studies are needed to confirm our findings.

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Affiliations

Ozra Tabatabaei-Malazy[1,2] · Edris Ardeshirlarijani[3] · Nazli Namazi[4] · Shekoufeh Nikfar[2,5,6,7] · Reza Baradar Jalili[8] · Bagher Larijani[2]

1 Non-Communicable Diseases Research Center, Endocrinology and Metabolism Population Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran

2 Endocrinology and Metabolism Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran

3 Simon Fraser University, Burnaby, Canada

4 Diabetes Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran

5 Personalized Medicine Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran

6 Evidence-based Evaluation of Cost-Effectiveness and Clinical Outcomes Group, The Institute of Pharmaceutical Sciences (TIPS), Tehran University of Medical Sciences, Tehran, Iran

7 Department of Pharmacoeconomics and Pharmaceutical Administration, Faculty of Pharmacy and Pharmaceutical Policy Research Center, Tehran University of Medical Sciences, Tehran, Iran

8 Department of Surgery, University of British Columbia, Vancouver, British Columbia, Canada