Débora Luana Ribeiro Pessoa
(Organizadora)

CIÊNCIAS FARMACÊUTICAS:

Prevenção, promoção, proteção e recuperação da saúde

Atena Editora
Ano 2022

Débora Luana Ribeiro Pessoa
(Organizadora)

CIÊNCIAS FARMACÊUTICAS:

Prevenção, promoção, proteção e recuperação da saúde

Atena Editora
Ano 2022

Editora chefe
Profª Drª Antonella Carvalho de Oliveira
Editora executiva
Natalia Oliveira
Assistente editorial
Flávia Roberta Barão
Bibliotecária
Janaina Ramos
Projeto gráfico
Camila Alves de Cremo
Daphynny Pamplona
Gabriel Motomu Teshima
Luiza Alves Batista
Natália Sandrini de Azevedo
Imagens da capa
iStock
Edição de arte
Luiza Alves Batista

Atena Editora
Ano 2022

Ciências farmacêuticas: prevenção, promoção, proteção e recuperação da saúde

Diagramação: Daphynny Pamplona
Correção: Yaiddy Paola Martinez
Indexação: Amanda Kelly da Costa Veiga
Revisão: Os autores
Organizadora: Débora Luana Ribeiro Pessoa

Dados Internacionais de Catalogação na Publicação (CIP)

C569 Ciências farmacêuticas: prevenção, promoção, proteção e recuperação da saúde / Organizadora Débora Luana Ribeiro Pessoa. – Ponta Grossa - PR: Atena, 2022.

Formato: PDF
Requisitos de sistema: Adobe Acrobat Reader
Modo de acesso: World Wide Web
Inclui bibliografia
ISBN 978-65-258-0050-9
DOI: https://doi.org/10.22533/at.ed.509221803

1. Farmácia. I. Pessoa, Débora Luana Ribeiro (Organizadora). II. Título.

CDD 615

Elaborado por Bibliotecária Janaina Ramos – CRB-8/9166

Atena Editora
Ponta Grossa – Paraná – Brasil
Telefone: +55 (42) 3323-5493
www.atenaeditora.com.br
contato@atenaeditora.com.br

Atena Editora
Ano 2022

DECLARAÇÃO DOS AUTORES

Os autores desta obra: 1. Atestam não possuir qualquer interesse comercial que constitua um conflito de interesses em relação ao artigo científico publicado; 2. Declaram que participaram ativamente da construção dos respectivos manuscritos, preferencialmente na: a) Concepção do estudo, e/ou aquisição de dados, e/ou análise e interpretação de dados; b) Elaboração do artigo ou revisão com vistas a tornar o material intelectualmente relevante; c) Aprovação final do manuscrito para submissão.; 3. Certificam que os artigos científicos publicados estão completamente isentos de dados e/ou resultados fraudulentos; 4. Confirmam a citação e a referência correta de todos os dados e de interpretações de dados de outras pesquisas; 5. Reconhecem terem informado todas as fontes de financiamento recebidas para a consecução da pesquisa; 6. Autorizam a edição da obra, que incluem os registros de ficha catalográfica, ISBN, DOI e demais indexadores, projeto visual e criação de capa, diagramação de miolo, assim como lançamento e divulgação da mesma conforme critérios da Atena Editora.

DECLARAÇÃO DA EDITORA

A Atena Editora declara, para os devidos fins de direito, que: 1. A presente publicação constitui apenas transferência temporária dos direitos autorais, direito sobre a publicação, inclusive não constitui responsabilidade solidária na criação dos manuscritos publicados, nos termos previstos na Lei sobre direitos autorais (Lei 9610/98), no art. 184 do Código Penal e no art. 927 do Código Civil; 2. Autoriza e incentiva os autores a assinarem contratos com repositórios institucionais, com fins exclusivos de divulgação da obra, desde que com o devido reconhecimento de autoria e edição e sem qualquer finalidade comercial; 3. Todos os e-book são *open access, desta forma* não os comercializa em seu site, sites parceiros, plataformas de *e-commerce,* ou qualquer outro meio virtual ou físico, portanto, está isenta de repasses de direitos autorais aos autores; 4. Todos os membros do conselho editorial são doutores e vinculados a instituições de ensino superior públicas, conforme recomendação da CAPES para obtenção do Qualis livro; 5. Não cede, comercializa ou autoriza a utilização dos nomes e e-mails dos autores, bem como nenhum outro dado dos mesmos, para qualquer finalidade que não o escopo da divulgação desta obra.

APRESENTAÇÃO

A obra “Ciências farmacêuticas: Prevenção, promoção, proteção e recuperação da saúde” que tem como foco principal a apresentação de trabalhos científicos diversos que compõe seus 14 capítulos, relacionados às Ciências Farmacêuticas e Ciências da Saúde. A obra abordará de forma interdisciplinar trabalhos originais, relatos de caso ou de experiência e revisões com temáticas nas diversas áreas de atuação do profissional Farmacêutico nos diferentes níveis de atenção à saúde.

O objetivo central foi apresentar de forma sistematizada e objetivo estudos desenvolvidos em diversas instituições de ensino e pesquisa do país. Em todos esses trabalhos a linha condutora foi o aspecto relacionado à atenção e assistência farmacêutica, produtos naturais e fitoterápicos, automedicação, saúde pública, entre outras áreas. Estudos com este perfil podem nortear novas pesquisas na grande área das Ciências Farmacêuticas.

Temas diversos e interessantes são, deste modo, discutidos aqui com a proposta de fundamentar o conhecimento de acadêmicos, mestres e todos aqueles que de alguma forma se interessam pelas Ciências Farmacêuticas, apresentando artigos que apresentam estratégias, abordagens e experiências com dados de regiões específicas do país, o que é muito relevante, assim como abordar temas atuais e de interesse direto da sociedade.

Deste modo a obra “Ciências farmacêuticas: Prevenção, promoção, proteção e recuperação da saúde” apresenta resultados obtidos pelos pesquisadores que, de forma qualificada desenvolveram seus trabalhos que aqui serão apresentados de maneira concisa e didática. Sabemos o quão importante é a divulgação científica, por isso evidenciamos também a estrutura da Atena Editora capaz de oferecer uma plataforma consolidada e confiável para estes pesquisadores exporem e divulguem seus resultados. Boa leitura!

Débora Luana Ribeiro Pessoa

SUMÁRIO

CAPÍTULO 4

ANTIOXIDANT EFFECTS OF VITAMINS SUPPLEMENTATION IN TYPE 2 DIABETES: A SYSTEMATIC REVIEW WITH META-ANALYSES OF RANDOMIZED CONTROLLED TRIALS

Data de aceite: 01/02/2022

Maria E. Balbi
Pharmaceutical Sciences Postgraduate Programme, Universidade Federal do Paraná
Curitiba, Brazil
ORCID ID 0000-0001-8210-9250

Fernanda S. Tonin
Pharmaceutical Sciences Postgraduate Programme, Universidade Federal do Paraná
Curitiba, Brazil
ORCID ID 0000-0003-4262-8608

Antonio E. M. Mendes
Pharmaceutical Sciences Postgraduate Programme, Universidade Federal do Paraná
Curitiba, Brazil
ORCID ID 0000-0002-5752-349X

Helena H. Borba
PhD. Department of Pharmacy, Universidade Federal do Paraná
Curitiba, Brazil
ORCID ID 0000-0001-9723-584X

Astrid Wiens
PhD. Department of Pharmacy, Universidade Federal do Paraná
Curitiba, Brazil
ORCID ID 0000-0003-4460-4044

Fernando Fernandez-Llimos
PhD. Research Institute for Medicines (iMed. ULisboa), Department of Social Pharmacy, Faculty of Pharmacy, Universidade de Lisboa
Lisbon, Portugal
ORCID ID 0000-0002-8529-9595

Roberto Pontarolo
PhD. Department of Pharmacy, Universidade Federal do Paraná
Curitiba, Brazil
ORCID ID 0000-0002-7049-4363

ABSTRACT: Aims: Vitamins are essential micronutrients with antioxidant potential that may represent a complementary treatment for patients with chronic diseases. Our aim was to assess the effects of vitamin supplementation on the antioxidant status in type 2 diabetes mellitus patients. **Methods:** We performed a systematic review with meta-analysis. Electronic searches were conducted in PubMed, Scopus, Web of Science (December 2017). Randomized controlled trials evaluating any vitamin or vitamin complex supplementation on antioxidant status as primary outcome (reduction of malodialdehyde – MDA; augmentation of glutathione peroxidase – GPx; changes in total antioxidant capacity – TAC, enhance in superoxide dismutase enzyme – SOD, and thiobarbituric acid reactive substances – TBARS) were included. Other outcomes of glycemic control were also evaluated. Pairwise meta-analyses were performed comparing vitamins against placebo. **Results:** Thirty trials fulfilled the inclusion criteria of the systematic review, but only 12 were able to be included in the meta-analyses of antioxidant outcomes. The main reported vitamins were B, C, D and E. Vitamin E was related to significantly reduction of blood glucose as well glycated hemoglobin, while both vitamins C and E were mainly referred in reducing MDA and TBARS and elevating GPx,

SOD and TAC. However, outcome report in this field is still inconsistent (e.g. lack of standard measures). **Conclusion:** The supplementation of vitamin E can be a valuable strategy for controlling diabetes complications and enhancing antioxidant capacity. The effects of other micronutrients should be further investigated in larger and well-designed trials to properly place these complementary therapies in clinical practice.
KEYWORDS: diabetes mellitus; antioxidant capacity; systematic review

HIGHLIGHTS:

- There are still divergences about the therapeutic potential of vitamins on metabolic disorders
- Vitamin E shows a promising antioxidant profile in diabetic patients
- Clinical trials should be more well-designed and properly report outcome data.

INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by an increase in blood glucose concentration (fasting blood glucose ≥126 mg/dL). Currently, there are 382 million patients with diabetes, and this number is expected to reach 592 million by 2035, being type 2 diabetes (T2DM) the most expressive form of the disease (1-3). The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) consensus statement on the management of T2DM recommend life-style changes (healthy diet and physical activity) in combination with metformin at the time of diagnosis, and addition of other medication in patients who do not achieve the desired glycemic control (1). Lowering glycated hemoglobin (HbA1c) to below 7% has clearly been shown as one of the primary endpoints to reduce microvascular complications of DM and possibly macrovascular disease (4).

Current evidence has further demonstrated that oxidative stress plays an important role in the pathogenesis of chronic diseases such as DM (5-7), and may diminish the antioxidative defense system of the body, increasing the oxidative load (3, 8, 9). Several studies have shown that individuals with low concentration of antioxidants are at increased risk of diabetes complications (10-14) and that T2DM is straightly associated with endothelial dysfunction (6, 7, 15). These conditions may develop macro and microvascular diseases such as retinopathy, nephropathy, lower extremity amputations, coronary artery and cardiovascular diseases (16-18), which are the main causes of morbidity and mortality worldwide (19, 20).

These damaging effects of oxidative stress are mainly caused by the production of free radicals of oxygen and reactive oxygen species (ROS), but these substances can be modified by enzymatic or non-enzymatic antioxidants such as superoxide dismutase, vitamins, minerals, polyphenols and some other molecules (6, 21, 22). A previous study

described that the supplementation with multivitamins in a population with high prevalence of micronutrient deficiency improved cerebrovascular disease mortality significantly (23). Other research groups have analyzed the antioxidant properties of natural products through chemical and/or biological methods. They have suggested that the consumption of food rich in antioxidants can retard or avoid the occurrence of many diseases (24, 25). Nevertheless, previous systematic reviews and individual randomized controlled trials (RCTs) that have measured the effect of vitamins supplementation on antioxidant status and glycemic control of diabetic patients have been conflicting, so that the benefit, or otherwise, of such supplementation remains still uncertain (26-33).

Thus, we aimed to conduct a systematic review and pairwise meta-analyses to gather current evidence on the effects of any vitamin supplementation on antioxidant status in T2DM patients, in order to elucidate its real benefits.

METHODS

We conducted and reported this systematic review and meta-analyses according to the Cochrane Recommendations and PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guideline (34, 35). All steps were performed by two independent reviewers and discrepancies were solved during consensus by a third author.

Search strategies and inclusion criteria

We searched for relevant articles in the databases PubMed, Scopus and Web of Science, without any time limit (updated December 18th, 2017). In addition, we conducted a manual search on the reference lists of the retrieved articles, reviews and trial registration databases to identify registers missed by the electronic search. Complete search strategies are presented in Supplement Material.

We included RCTs assessing adult patients (over 18 years old) of any gender with any stage of type 2 diabetes condition that have evaluated plasmatic antioxidant parameters or of oxidative stress. Patients received vitamin (types A and/or B complex and/or C and/or D and/or E or variants administered alone or in combination with other vitamins, micronutrients or minerals) irrespective of form, dosage, duration or route of administration compared with placebo or no treatment or other vitamins (active control).

Two researchers independently screened titles and abstracts of the articles retrieved by the systematic review to identify irrelevant records. In a second stage, full text articles were evaluated to identify any of the following exclusion criteria: non-randomized controlled trials (type of studies); other interventions than vitamins; individuals aged under 18 years; different populations (non-type 2 diabetes); different outcomes measure other than antioxidant-related; trials published in non-roman characters.

Data extraction and quality assessment

The following data were independent extracted from the included studies by two researchers: baseline characteristics (authors names, year of publication, study design, country, sample size, gender, age, patients' condition, trial duration); methodological aspects; and clinical outcomes of interest. For primary outcome studies should report alterations in plasma antioxidant parameters or oxidative stress, such: as vitamins levels, antioxidant enzymes levels (superoxide dismutase (SOD), glutathione peroxidase (GPx) and catalase (CAT)), oxidative stress biomarkers (e.g. harmful products MDA (malondialdehyde) and thiobarbituric acid reactive substances (TBARS)) and changes in plasma total antioxidant capacity (TAC). Other changes in anthropometric and glycemic parameters such as fast blood glucose and HbA1c reduction, as core outcome set for diabetes control, were also collected, when available.

Included studies were evaluated with two different instruments: the Jadad score and the Cochrane Collaboration's tool for assessing the Risk of Bias (34), in order to evaluate studies' methodological aspects such as properly randomization, blinding, account for patients withdrawals and dropouts and possible related bias that may affect data interpretation.

Statistical analyses

When possible, pairwise meta-analyses of the included RCTs using placebo as comparator were performed for the main outcome measures. These analyses were conducted using the software Review Manager version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).

For each meta-analysis we used the random effects model and the inverse variance (IV) method to interpolate the mean differences (MD) or standardized (std.) mean differences (SMD) of each study from baseline. Results were reported with a 95% confidence interval (CI). A p value less than 0.05 (two-tailed) was considered indicative of a statistically significant difference between groups. The heterogeneity between-trial was assessed using the inconsistency index value (I^2) ($I^2 > 50\%$ - high and significant heterogeneity)(34). We also conducted sensitivity analyses to test the robustness of the results to evaluate the impact of any study on data heterogeneity. The analyses consisted of the hypothetical sequential removal of studies of the meta-analysis. When possible, subgroup analyses were also performed.

RESULTS

After the systematic search conducted in the three databases, 1,570 records were retrieved and 196 were excluded as duplicates. During study's title and abstract reading

(screening), 1,243 records were excluded and 104 were considered for full-text appraisal, of which 25 RCTs were suitable for final analyses. Five articles were added by manual searches, finally encompassing 30 RCTs (36-66) (Figure 1). The main characteristics of included studies are provided in Table 1.

All studies involved patients diagnosed with T2DM (n=1,430) and were conducted mainly in Iran (n=9 trials); followed by United Kingdom (n=4) and United States of America (n=3). Evaluated treatments comprised: vitamin B (n=1 study), vitamin C (n=10); vitamin D (n=7); vitamin E (n=11), and mixture of vitamins B, C and E (n=1). In four of these trials (13.3%), vitamins were delivered by food fortification (oil or yogurt) (43, 55, 59, 62). Placebo or negative control were the main comparators in 29 studies (96.7%), while eight trials (26.7%) included head-to-head comparisons. Duration of treatment ranged from two to 24 weeks and patients age ranged from 46 to 72 years.

Overall, methodological quality of included trials was low-moderate, with a mean Jadad Score of 2.7 (range - 1 to 5). All studies scored on randomization, but only 20.0% of them described properly these methods. Almost all trials (90.0%) accounted for patient's withdrawals or dropouts, and half of studies were double-blinded. However, only two trials described the blinding methods. For the Risk of Bias Tool (see supplement material), trials were considered of low risk of bias (> 75%) in the domains of randomization, incomplete outcome data and free of selective reporting. Allocation concealment was considered unclear in 25 trials (86.2%), and for blinding of participants or outcomes studies often failed to provide details. Overall, 70.0% of trials were funded by industries or reported conflict of interest.

Considering the primary outcomes of interest related to antioxidant status, twelve studies were able to be included in the meta-analyses of intervention (vitamin) versus placebo/control. Not all studies were statistically evaluated since outcomes were not comparable (e.g. lack of raw data). Also, gathering evidence especially on antioxidant potential was hampered due to the lack of standardization of outcomes report in the clinical trials (e.g. inconsistent report, different measures, scales and units).

Meta-analyses were obtained for augmentation of GPx levels (Units / gram of Hemoglobin - U/g Hb), plasma MDA (nmol/L) and TBARS (μmol/L) reductions, and favorable changes in TAC (mmol/L) and SOD (U/g Hb). In these cases, no subgroup analyses were performed due to the limit number of studies. Overall, results were statistically different against placebo and favored the use of vitamins with values of MD 9.40 (95% CI [7.79; 11.00]) for GPx and MD -0.53 (95% CI [-0.81; -0.25]) for MDA, with I^2 values of 44% and 47%, respectively. Vitamins were also superior to placebo in reducing TBARS with an overall effect size of SMD -4.84 (95% CI [-6.01; -3.67]) ($I^2 = 54\%$) and in increasing TAC (SMD 0.38 [0.11; 0.65]) and SOD levels (SMD 0.64 [0.11; 1.17]). These positive results came mostly from studies where the interventions were vitamin E (n=7 trials)(39, 44, 47, 50, 56, 62, 65); vitamin C (n=2)(49, 52) and vitamin D (n=2)(55, 59) (see Figure 2).

The meta-analyses of the glycemic control parameters (13 included trials) are shown in figures 3 and 4. No statistical differences were observed in subgroup analyses comparing vitamins C or D with placebo. However, for both of the outcomes of mean change in blood glucose (mg/dL) and reduction of HbA1c (in percentage), the effects of vitamin E were significantly better when compared to control (values of MD -13.89 (95% CI [-19.89; -7.89]) and MD -0.47 (95% CI [-0.69; -0.26]), respectively).

The moderate-high heterogeneity of some meta-analyses (I^2 ranging from 15% to 71%) were caused by more than one study and can be acceptable in this context. Sensitivity analyses were conducted with all the meta-analyses (data not shown) and despite the sequential hypothetical removal of studies with reduction in the heterogeneity, results remained unchanged. Differences in the intrinsic characteristics of the included studies, the conduction and design of trials with low quality, sample sizes and patient's conditions with possible comorbidities and different pharmacological treatments, type of intervention and differences in outcomes measures can explain these discrepancies.

DISCUSSION

Our study is the first systematic review with meta-analysis that incorporates the available evidence of vitamin supplementation in T2DM patients for the improvement of antioxidant status in different ways (GPx, SOD and TAC levels augmentation and reduction in MDA and TBARS products). Previous studies have focused on glycemic control, insulin resistance and changes in endothelial functions (28, 30-33).

Vitamins are essential micronutrients acquired primarily through diet (e.g. consumption of fruits, vegetables, oils, nuts), but also are readily available as over-the-counter drugs. Since the natural intake of these vitamins may not be daily sufficient – notably for patients with chronic diseases – the supplementation may represent a common, accessible, complementary and easy treatment, especially for enhance antioxidant status and improve body defense (8, 67, 68). Potential antioxidant vitamins such as C and E are found decreased in diabetic subjects, possibly due to an increased need to control the excessive oxidative stress produced by abnormalities in glucose metabolism and lipid peroxidation (69). Despite guidelines and protocols did not specifically recommend the use of multivitamins for the general healthy population, it is indicated that some specific diseases might benefit from its supplementation (42, 69). However, few recommendations exist for T2DM.

Our current results revealed that supplementation of certain vitamins in T2DM, especially vitamin E, can produce significant impact on parameters of oxidative stress and in glycemic control, which may positively benefit patients. Vitamin C was more related to changes in antioxidant status, while few evidence was found for the other vitamins (e.g. D or B).

These beneficial effects of vitamin E may be explained by the reduction of the damaging effects of free radicals on structural and functional components of cells and vessels walls (30). It is believed that diabetes is associated with increased oxidative stress as increased blood concentrations of thiobarbituric acid reactive substances and serum malonaldehyde, end products of lipid peroxidation (70). As consequences, adverse physiological effects include leakiness of cell membranes by altering structural integrity of membrane; inactivation of membrane bound enzymes and surface receptor and the involvement of oxidized LDL. When the total antioxidant status is high and enough to combat the oxidative stress, the MDA and TBARS levels are in the normal limits and vice-versa. (12, 26, 71). Antioxidants can decrease the oxidative damage directly via reacting with free radicals or indirectly by inhibiting the activity or expression of free radical (21, 72). TAC levels in plasma represent the sum of both exogenous as well as endogenous antioxidants activities. Thus, the decreased TAC status and increased MDA and TBARS levels could be taken as an early marker of the pathogenesis of complications in T2DM (26, 68, 71).

Non-enzymatic antioxidants such as vitamins C and E and glutathione enzyme interrupt the free radical chain reactions. The combination of these vitamins appears to be promising. Despite only one RCT evaluating a mixed vitamin complex was found in our systematic review (42), previous studies reported that antioxidant combinations can be an appropriate formula for the management of diabetes (72, 73). A three-month study on the supplementation of vitamins C and E showed that patients decreased blood glucose while increasing SOD and glutathione levels (69, 74). Moreover, the long-term use of dietary supplements, including multivitamin/mineral complex showed better conditions for C-reactive protein, HDL cholesterol, triacylglycerides, serum homocystein, blood pressure and incidence of diabetes (75, 76). However, alone, vitamin C did not present a greater profile than vitamin E.

In the literature, vitamin D is related to gene expression control that may trigger a biological response to oxidative stress, such as inhibiting nitric oxide synthase (iNOS) or increasing gluthatione levels (5, 77). There is evidence in humans and animal models suggesting that vitamin D may play an important role in modifying the risk of diabetes (5, 78). Low vitamin D status is associated with future macrovascular events in patients with T2DM. This association may be the result of the link between vitamin D status and renin-angiotensin system, endothelial function, blood pressure, or even chronic inflammation (31, 77, 79). However, our results were scarce on defining vitamin D antioxidant profile, since few RCTs involving this micronutrient were included. Besides, some trials (43, 55, 59, 62) did not employed a directly drug supplementation, but incorporated the vitamin in food (e.g. oil, yogurt), which may affect final results.

Moreover, because total daily dosage of vitamins intake and treatment duration were variable among studies, effects on antioxidant and glycemic profiles may be underestimated. Regimens for vitamin C varies from 500 to 3000 mg/day; for vitamin E ranges from 400 to

1600 IU/day and for vitamin D doses were of 500 to 200,000 IU/day. Nevertheless, very few treatment withdrawals and dropouts as well adverse events due to supplementation were reported in all the clinical trials. Longer periods trials with reasonably lower daily dose may increase the intracellular concentration of vitamins and result in a sufficient effect that should be further evaluated.

Despite these results, the assessment of the outcomes related to antioxidant status was limited by the small number of studies properly reporting data. Moreover, methodological aspects of the included trials revealed low-moderate quality, especially concerning accurately description of randomization and blinding. It is noteworthy that methodological errors (e.g. poor blinding or randomization) allow factors such as the placebo effect or selection bias to adversely affect the results of the study, and thus should be carefully analyzed (80, 81).

The marked heterogeneity in the outcomes report of oxidative stress and antioxidant capacity might be due the lack of standardization in the selection and/or measurement of the outcome in clinical trials. Different measures and units (e.g., enzymes levels (catalase, superoxide dismutase); FRAP - ferric reducing ability of plasma assay; ORAC - oxygen radical absorbance capacity assay; TAS - total antioxidant status, among others) are usually employed (82, 83). This can be partly justified because of the range of substances and antioxidant components in the organism together with the difficulty in measuring all at once. Further, inherent variables such as differences between subjects and diseases and comorbidities stages should be taken into account (12, 83). The issue of lack of outcomes standardization is common to different areas (84), but has been associated with a bad reporting practice – outcome switching, and hampers comparisons between interventions (84, 85). Thus, the development of a core outcome set related to antioxidant status in chronic diseases such as DM is an important component of studies design and can minimize bias and reduce inconsistency of evidence. Measures such as TAC, TBARS and MDA could be employed as standard.

Our study has some limitations. We included in the analyses RCTs with differences in methodological design and populations characteristics (e.g. age, gender, disease stage and comorbidities, diabetes treatments, study duration) and none of them were sufficiently powered because the relatively small number of participants. There was some difficulty to find and gather trials of the same vitamin or vitamin complex assessing similar outcomes. We were able to statistically analyze three vitamins (C, D and E), but other micronutrients and vitamin combinations (especially vitamins C and E) should be better investigated. Subgroup meta-analyses were poorly obtained.

We strongly recommend that further well-designed, large-scale, long-term head-to-head controlled trials and meta-analyses be carried out to demonstrate the effects of individual or multivitamins supplementations on T2DM, since previous results are promising.

CONCLUSION

The consumption of vitamin E (alone or in combination) promotes health benefits since it affects plasma antioxidant capacity, concentration of enzymes and reduce MDA e TBARS levels. Considering that T2DM patients have a high risk of experiencing micro and macrovascular complications, an alternative strategy for metabolic control, besides the combination of diet, exercise and medication, would be by the potential daily supplementation with vitamins. Hence, these substances may represent a step forward in disease management and prevent the occurrence of these complications. Further studies should be conducted to strength this evidence, especially for defining doses and regimen of vitamin E and support its use in daily practice.

TABLES AND FIGURES

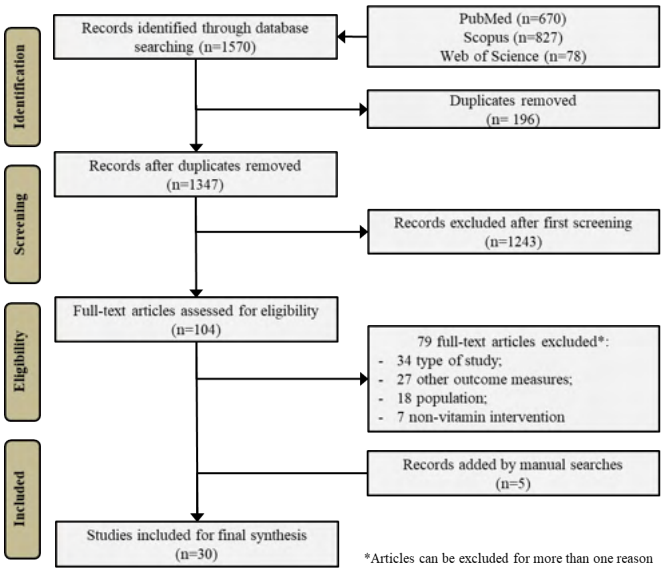
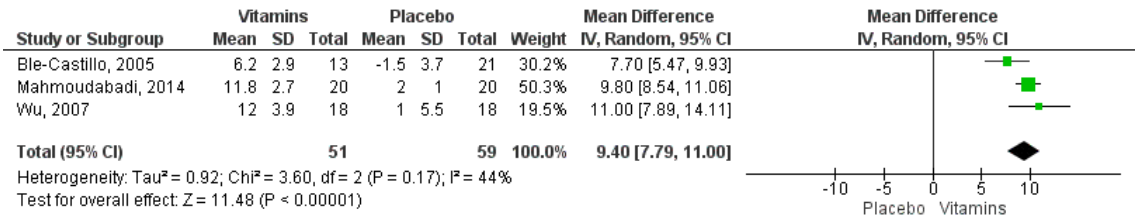
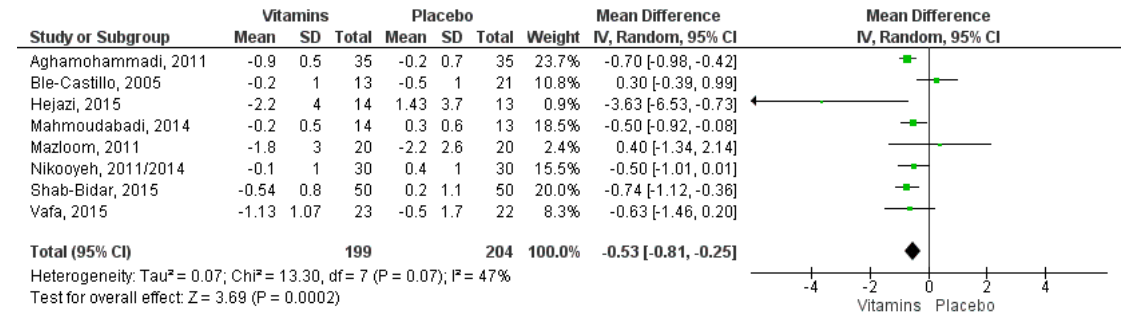


Figure 1. Flowchart of the systematic review process.

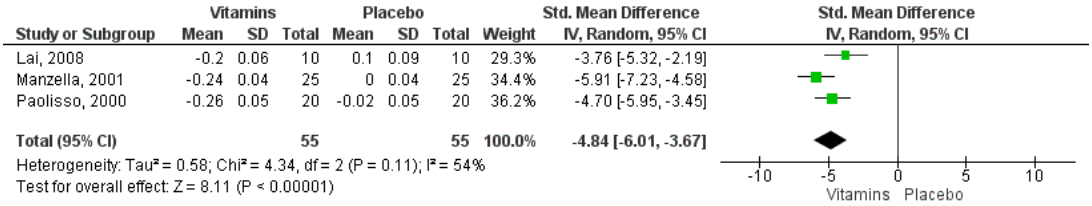
(A)



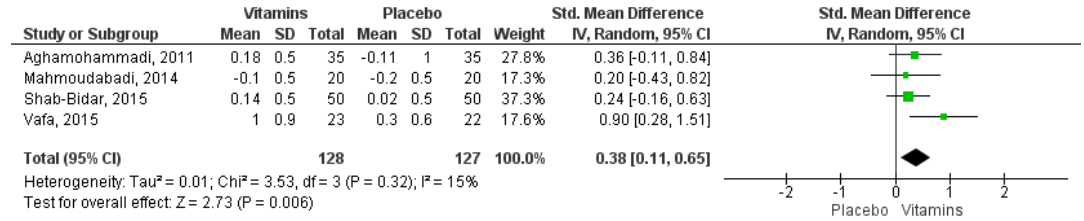
(B)



(C)



(D)



(E)

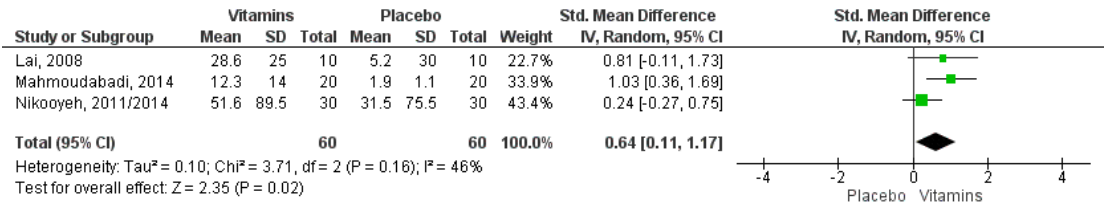


Figure 2. Forest plots for the outcomes: (A) augmentation of GPx level (U/g Hb); (B) reduction of MDA (nmol/L); (C) reduction of TBARS (μmol/L); (D) changes in TAC (mmol/L); (E) changes in SOD (U/g). Statistical method: Mean difference (MD) and Std. Mean Difference (SMD), IV, Random, 95% confidence interval.

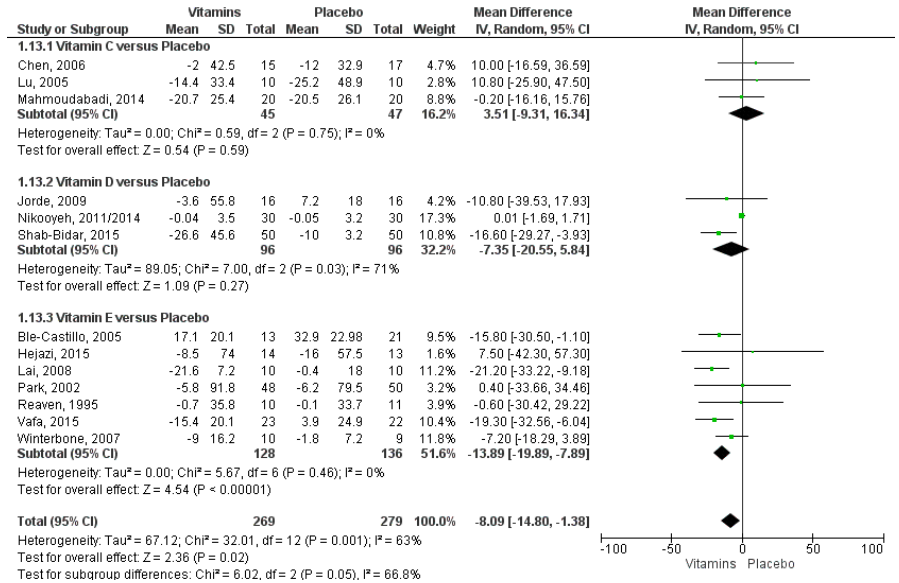


Figure 3. Forest plot for the outcome measure of blood glucose mean change from baseline (mg/dL). Statistical method: Mean difference (MD), IV, Random, 95% confidence interval.

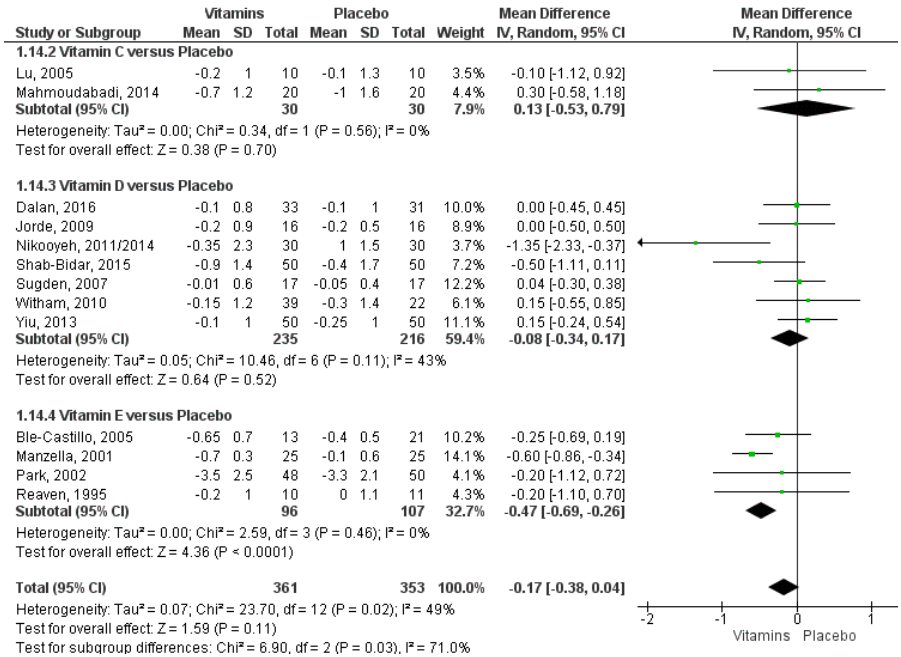


Figure 4. Forest plot for the outcome measure of HbA1c mean change from baseline (%). Statistical method: Mean difference (MD), IV, Random, 95% confidence interval.

Author, year	Country	Treatments	N	Duration	Age (years)	Male %	Jadad Score
Aghamohammadi, 2011 (36)	Iran	Vitamin B9 5 mg/day Placebo	70	8 weeks	58.7 ± 7.2 55.6 ± 9.3	100	3
Anderson, 2006 (37)	Wales	Vitamin C 1,000 mg/day Placebo	20	6 weeks	52.7 ± 6.9 53.6 ± 7.9	40.0	2
Antoniades, 2004 (38)	Greece	Vitamin C 2,000 mg/day Placebo	17	4 weeks	48.5 ± 6.6 52.6 ± 5.9	58.8	1
Ble-Castillo, 2005 (39)	United States	Vitamin E 800 IU/day Placebo	33	6 weeks	51.3 ± 14.0 55.3 ± 11.6	0	2
Chen, 2006 (40)	United States	Vitamin C 800 mg/day Placebo	32	4 weeks	50.0 ± 1.0	40.6	3
Dalan, 2016 (41)	Singapore	Vitamin D 4,000 IU/day Vitamin D 2,000 IU/day Placebo	64	16 weeks	52.2 ± 8.2 54.8 ± 10.8	51.6	5
Gariballa, 2013 (42)	Arab Emirates	Vitamin complex (B, C, E) Placebo	100	12 weeks	52 (44–56) 51 (42-60)	41.0	2
Haghighat, 2014 (43)	Iran	Vitamin E enriched canola oil 15 ml/day Placebo oil	45	8 weeks	55.9 ± 5.9 55.2 ± 5.6	26.7	2
Hejazi, 2015 (44)	Iran	Vitamin E 400 IU/day Placebo	27	6 weeks	48.0 ± 6.3 46.6 ± 7.6	26.0	3
Jamalan, 2015 (45)	Iran	Vitamin C 1,000 mg/day Vitamin E 300 mg/day	80	4 weeks	52.0 ± 8.0	100	2
Jorde, 2009 (46)	Norway	Vitamin D 40,000 IU/week Placebo	32	24 weeks	57.7 ± 9.7 54.8 ± 5.9	56.2	2
Lai, 2008 (47)	Japan	Chromium 1000 μg Vitamin E 800 IU + chromium Placebo	30	24 weeks	53.2 ± 2.0 51.5 ± 1.7 50.5 ± 1.9	46.7	3
Lu, 2005 (48)	Sweden	Vitamin C 3,000 mg/day Placebo	20	2 weeks	-	60.0	2
Mahmoudabadi, 2014 (49)	Iran	Eicosanpentaenoic acid 500mg/day Vitamin C 200mg/day Vitamin C + eicosanpentaenoic acid Placebo	81	8 weeks	54.0 ± 5.0 53.0 ± 5.0 52.0 ± 6.0 50.0 ± 8.0	100	2
Manzella, 2001 (50)	Italy	Vitamin E 600 mg/day Placebo	50	16 weeks	64.3 ± 4.7 65.1 ± 3.9	-	3
Mason, 2016 (51)	Australia	Vitamin C 1,000mg/day Placebo	13	16 weeks	59.4 ± 3.5	92.3	3
Mazloom, 2011 (52)	Iran	Vitamin C 1,000mg/day Placebo	27	6 weeks	47.0 ± 8.9 46.6 ± 7.6	42.1	2
Mullan, 2002 (53)	United Kingdom	Vitamin C 500mg/day Placebo	30	4 weeks	61.0 ± 6.5 57.9 ± 6.6	73.4	3

Author, year	Country	Treatments	N	Duration	Age (years)	Male %	Jadad Score
Nikooyeh, 2011/2014 (54, 55)	Iran	Yogurt (150 mg calcium/250 mL) Vitamin D fortified (150 mg calcium + 500 IU/250 mL) Vitamin D fortified (250 mg of calcium + 500 IU/250 mL) *Two bottles/day = 500 mL/day	90	12 weeks	50.8 ± 6.6 51.4 ± 5.4 49.9 ± 6.2	38.9	2
Paolisso, 2000 (56)	Italy	Vitamin E 600 mg/day Placebo	40	8 weeks	58.3 ± 6.4 56.7 ± 5.3	52.5	3
Park, 2002 (57)	Korea	Vitamin E 200 mg/day Placebo	98	8 weeks	49.4 ± 9.3 49.5 ± 10.1	59.2	2
Reaven, 1995 (58)	United States	Vitamin E 1,600 IU/day Placebo	21	10 weeks	60.8 ± 6.1 61.8 ± 8.4	100	2
Shab-Bidar, 2015 (59)	Iran	Vitamin D fortified Yogurt 500 UI, 500ml/day Yogurt	100	12 weeks	52.6 ± 6.3 52.4 ± 8.4	43.0	3
Sugden 2007 (60)	United Kingdom	Vitamin D 100 000 UI/day Placebo	34	8 weeks	64.9 ± 10.3 63.5 ± 9.5	52.9	5
Tessier, 2009 (61)	Canada	Vitamin C 500 mg/day Vitamin C 1000 mg/day Placebo	36	12 weeks	72.0 ± 5.0 72.0 ± 4.0 71.0 ± 4.0	22.2	3
Vafa, 2015 (62)	Iran	Vitamin E enriched canola oil 15 ml/day Canola oil	45	8 weeks	55.9 ± 5.9 55.2 ± 5.6	73.3	4
Winterbone, 2007 (63)	United Kingdom	Vitamin E 1,200 IU α-tocopherol/day Placebo	19	4 weeks	62.7 ± 1.8 61.9 ± 1.9	100	2
Witham, 2010 (64)	United Kingdom	Vitamin D3 100,000 IU/day Vitamin D3 200,000 IU/day Placebo	41	16 weeks	65.3 ± 11.1 63.3 ± 9.6 66.7 ± 9.7	67.2	3
Wu, 2007 (65)	Australia	Vitamin E α-tocopherol 500 mg/day Vitamin E mixed tocopherols 500 mg/day Placebo	55	6 weeks	64.0 ± 7.0 58.0 ± 4.0 62.0 ± 7.0	74.5	2
Yiu, 2013 (66)	China	Vitamin D 500 IU/day Placebo	100	12 weeks	65.8 ± 7.3 64.9 ± 8.9	50.0	4

REFERENCES

1. American Diabetes A. Standards of medical care in diabetes--2009. Diabetes care. 2009;32 Suppl 1:S13-61.

2. IDF Diabetes. 7th ed. Federation ID, editor. Brussels, Belgium2015.

3. Jafari T, Fallah AA, Azadbakht L. Role of dietary n-3 polyunsaturated fatty acids in type 2 diabetes: a review of epidemiological and clinical studies. Maturitas. 2013;74(4):303-8.

4. Cobitz AR, Ambery P. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. Response to Nathan et al. Diabetes care. 2009;32(5):e58; author rely e9.

5. Pittas AG, Lau J, Hu FB, Dawson-Hughes B. The role of vitamin D and calcium in type 2 diabetes. A systematic review and meta-analysis. The Journal of clinical endocrinology and metabolism. 2007;92(6):2017-29.

6. Johansen JS, Harris AK, Rychly DJ, Ergul A. Oxidative stress and the use of antioxidants in diabetes: linking basic science to clinical practice. Cardiovascular diabetology. 2005;4:5.

7. Ceriello A, Testa R, Genovese S. Clinical implications of oxidative stress and potential role of natural antioxidants in diabetic vascular complications. Nutrition, metabolism, and cardiovascular diseases : NMCD. 2016;26(4):285-92.

8. Ratnam DV, Ankola DD, Bhardwaj V, Sahana DK, Kumar MN. Role of antioxidants in prophylaxis and therapy: A pharmaceutical perspective. Journal of controlled release : official journal of the Controlled Release Society. 2006;113(3):189-207.

9. Manna P, Jain SK. Obesity, Oxidative Stress, Adipose Tissue Dysfunction, and the Associated Health Risks: Causes and Therapeutic Strategies. Metabolic syndrome and related disorders. 2015;13(10):423-44.

10. Gey KF, Moser UK, Jordan P, Stahelin HB, Eichholzer M, Ludin E. Increased risk of cardiovascular disease at suboptimal plasma concentrations of essential antioxidants: an epidemiological update with special attention to carotene and vitamin C. The American journal of clinical nutrition. 1993;57(5 Suppl):787S-97S.

11. Gey KF, Puska P, Jordan P, Moser UK. Inverse correlation between plasma vitamin E and mortality from ischemic heart disease in cross-cultural epidemiology. The American journal of clinical nutrition. 1991;53(1 Suppl):326S-34S.

12. Sankhla M, Sharma TK, Mathur K, Rathor JS, Butolia V, Gadhok AK, et al. Relationship of oxidative stress with obesity and its role in obesity induced metabolic syndrome. Clinical laboratory. 2012;58(5-6):385-92.

13. Kataja-Tuomola MK, Kontto JP, Mannisto S, Albanes D, Virtamo J. Intake of antioxidants and risk of type 2 diabetes in a cohort of male smokers. European journal of clinical nutrition. 2011;65(5):590-7.

14. Kositsawat J, Freeman VL. Vitamin C and A1c relationship in the National Health and Nutrition Examination Survey (NHANES) 2003-2006. Journal of the American College of Nutrition. 2011;30(6):477-83.

15. Calles-Escandon J, Cipolla M. Diabetes and endothelial dysfunction: a clinical perspective. Endocrine reviews. 2001;22(1):36-52.

16. Hink U, Tsilimingas N, Wendt M, Munzel T. Mechanisms underlying endothelial dysfunction in diabetes mellitus: therapeutic implications. Treatments in endocrinology. 2003;2(5):293-304.

17. Duckworth WC. Hyperglycemia and cardiovascular disease. Current atherosclerosis reports. 2001;3(5):383-91.

18. Sasaki S, Inoguchi T. The role of oxidative stress in the pathogenesis of diabetic vascular complications. Diabetes & metabolism journal. 2012;36(4):255-61.

19. Stamler J, Vaccaro O, Neaton JD, Wentworth D. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. Diabetes care. 1993;16(2):434-44.

20. Beckman JA, Creager MA, Libby P. Diabetes and atherosclerosis: epidemiology, pathophysiology, and management. Jama. 2002;287(19):2570-81.

21. Lamb RE, Goldstein BJ. Modulating an oxidative-inflammatory cascade: potential new treatment strategy for improving glucose metabolism, insulin resistance, and vascular function. International journal of clinical practice. 2008;62(7):1087-95.

22. Evans JL, Maddux BA, Goldfine ID. The molecular basis for oxidative stress-induced insulin resistance. Antioxidants & redox signaling. 2005;7(7-8):1040-52.

23. Mark SD, Wang W, Fraumeni JF, Jr., Li JY, Taylor PR, Wang GQ, et al. Lowered risks of hypertension and cerebrovascular disease after vitamin/mineral supplementation: the Linxian Nutrition Intervention Trial. American journal of epidemiology. 1996;143(7):658-64.

24. White PA, Oliveira RC, Oliveira AP, Serafini MR, Araujo AA, Gelain DP, et al. Antioxidant activity and mechanisms of action of natural compounds isolated from lichens: a systematic review. Molecules. 2014;19(9):14496-527.

25. Singh R, Devi S, Gollen R. Role of free radical in atherosclerosis, diabetes and dyslipidaemia: larger-than-life. Diabetes/metabolism research and reviews. 2015;31(2):113-26.

26. Fenercioglu AK, Saler T, Genc E, Sabuncu H, Altuntas Y. The effects of polyphenol-containing antioxidants on oxidative stress and lipid peroxidation in Type 2 diabetes mellitus without complications. Journal of endocrinological investigation. 2010;33(2):118-24.

27. Tabatabaei-Malazy O, Nikfar S, Larijani B, Abdollahi M. Influence of ascorbic acid supplementation on type 2 diabetes mellitus in observational and randomized controlled trials; a systematic review with meta-analysis. Journal of pharmacy & pharmaceutical sciences : a publication of the Canadian Society for Pharmaceutical Sciences, Societe canadienne des sciences pharmaceutiques. 2014;17(4):554-82.

28. Montero D, Walther G, Stehouwer CD, Houben AJ, Beckman JA, Vinet A. Effect of antioxidant vitamin supplementation on endothelial function in type 2 diabetes mellitus: a systematic review and meta-analysis of randomized controlled trials. Obesity reviews : an official journal of the International Association for the Study of Obesity. 2014;15(2):107-16.

29. Sarmento RA, Silva FM, Sbruzzi G, Schaan BD, Almeida JC. Antioxidant micronutrients and cardiovascular risk in patients with diabetes: a systematic review. Arquivos brasileiros de cardiologia. 2013;101(3):240-8.

30. Ashor AW, Siervo M, Lara J, Oggioni C, Afshar S, Mathers JC. Effect of vitamin C and vitamin E supplementation on endothelial function: a systematic review and meta-analysis of randomised controlled trials. The British journal of nutrition. 2015;113(8):1182-94.

31. George PS, Pearson ER, Witham MD. Effect of vitamin D supplementation on glycaemic control and insulin resistance: a systematic review and meta-analysis. Diabetic medicine : a journal of the British Diabetic Association. 2012;29(8):e142-50.

32. Suksomboon N, Poolsup N, Sinprasert S. Effects of vitamin E supplementation on glycaemic control in type 2 diabetes: systematic review of randomized controlled trials. Journal of clinical pharmacy and therapeutics. 2011;36(1):53-63.

33. Xu R, Zhang S, Tao A, Chen G, Zhang M. Influence of vitamin E supplementation on glycaemic control: a meta-analysis of randomised controlled trials. PloS one. 2014;9(4):e95008.

34. Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0: Cochrane 2011.

35. Moher D, Liberati A, Tetzlaff J, Altman DG. The PRISMA Group. Preferred reporting items for systematic reviews and metaanalyses: the PRISMA statement. J Clin Epidemiol 2009;62:1006-12.

36. Aghamohammadi V, Gargari BP, Aliasgharzadeh A. Effect of folic acid supplementation on homocysteine, serum total antioxidant capacity, and malondialdehyde in patients with type 2 diabetes mellitus. Journal of the American College of Nutrition. 2011;30(3):210-5.

37. Anderson RA, Evans LM, Ellis GR, Khan N, Morris K, Jackson SK, et al. Prolonged deterioration of endothelial dysfunction in response to postprandial lipaemia is attenuated by vitamin C in Type 2 diabetes. Diabetic medicine : a journal of the British Diabetic Association. 2006;23(3):258-64.

38. Antoniades C, Tousoulis D, Tountas C, Tentolouris C, Toutouza M, Vasiliadou C, et al. Vascular endothelium and inflammatory process, in patients with combined Type 2 diabetes mellitus and coronary atherosclerosis: the effects of vitamin C. Diabetic medicine : a journal of the British Diabetic Association. 2004;21(6):552-8.

39. Ble-Castillo JL, Carmona-Diaz E, Mendez JD, Larios-Medina FJ, Medina-Santillan R, Cleva-Villanueva G, et al. Effect of alpha-tocopherol on the metabolic control and oxidative stress in female type 2 diabetics. Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie. 2005;59(6):290-5.

40. Chen H, Karne RJ, Hall G, Campia U, Panza JA, Cannon RO, 3rd, et al. High-dose oral vitamin C partially replenishes vitamin C levels in patients with Type 2 diabetes and low vitamin C levels but does not improve endothelial dysfunction or insulin resistance. American journal of physiology Heart and circulatory physiology. 2006;290(1):H137-45.

41. Dalan R, Liew H, Assam PN, Chan ES, Siddiqui FJ, Tan AW, et al. A randomised controlled trial evaluating the impact of targeted vitamin D supplementation on endothelial function in type 2 diabetes mellitus: The DIMENSION trial. Diabetes & vascular disease research. 2016;13(3):192-200.

42. Gariballa S, Afandi B, Abu Haltem M, Yassin J, Alessa A. Effect of antioxidants and B-group vitamins on risk of infections in patients with type 2 diabetes mellitus. Nutrients. 2013;5(3):711-24.

43. Haghighat NV, M.; Eghtesadi, S.; Heidari, I.; Hosseini, A.; Rostami, A. The Effects of Tocotrienols Added to Canola Oil on Microalbuminuria, Inflammation, and Nitrosative Stress in Patients with Type 2 Diabetes: A Randomized, Double-blind, Placebo-controlled Trial. Int J Prev Med. 2014;5(5):617-23.

44. Hejazi N, Dabbaghmanesh M, Mazloom Z, Dashtabi A. Effects of Vitamin E on Fasting and Postprandial Oxidative Stress, Inflammatory Markers, Glucose Status, Insulin Resistance, Blood Pressure and Pulse Rate in Type-2 Diabetic Patients: A Randomized Clinical Trial. GMJ. 2015;4(3):67-74.

45. Jamalan M, Rezazadeh M, Zeinali M, Ghaffari MA. Effect of ascorbic acid and alpha-tocopherol supplementations on serum leptin, tumor necrosis factor alpha, and serum amyloid A levels in individuals with type 2 diabetes mellitus. Avicenna journal of phytomedicine. 2015;5(6):531-9.

46. Jorde R, Figenschau Y. Supplementation with cholecalciferol does not improve glycaemic control in diabetic subjects with normal serum 25-hydroxyvitamin D levels. European journal of nutrition. 2009;48(6):349-54.

47. Lai MH. Antioxidant effects and insulin resistance improvement of chromium combined with vitamin C and e supplementation for type 2 diabetes mellitus. Journal of clinical biochemistry and nutrition. 2008;43(3):191-8.

48. Lu Q, Bjorkhem I, Wretlind B, Diczfalusy U, Henriksson P, Freyschuss A. Effect of ascorbic acid on microcirculation in patients with Type II diabetes: a randomized placebo-controlled cross-over study. Clinical science. 2005;108(6):507-13.

49. Mahmoudabadi MM, Rahbar AR. Effect of EPA and vitamin C on superoxide dismutase, glutathione peroxidase, total antioxidant capacity and malondialdehyde in type 2 diabetic patients. Oman medical journal. 2014;29(1):39-45.

50. Manzella D, Barbieri M, Ragno E, Paolisso G. Chronic administration of pharmacologic doses of vitamin E improves the cardiac autonomic nervous system in patients with type 2 diabetes. The American journal of clinical nutrition. 2001;73(6):1052-7.

51. Mason SA, Della Gatta PA, Snow RJ, Russell AP, Wadley GD. Ascorbic acid supplementation improves skeletal muscle oxidative stress and insulin sensitivity in people with type 2 diabetes: Findings of a randomized controlled study. Free radical biology & medicine. 2016;93:227-38.

52. Mazloom ZH, N.; Dabbaghmanesh, M. H.; Tabatabaei, H. R.; Ahmadi, A.; Ansar, H. Effect of vitamin C supplementation on postprandial oxidative stress and lipid profile in type 2 diabetic patients. Pakistan Journal of Biological Sciences. 2011;14(19):900-4.

53. Mullan BA, Young IS, Fee H, McCance DR. Ascorbic acid reduces blood pressure and arterial stiffness in type 2 diabetes. Hypertension. 2002;40(6):804-9.

54. Nikooyeh B, Neyestani TR, Farvid M, Alavi-Majd H, Houshiarrad A, Kalayi A, et al. Daily consumption of vitamin D- or vitamin D + calcium-fortified yogurt drink improved glycemic control in patients with type 2 diabetes: a randomized clinical trial. The American journal of clinical nutrition. 2011;93(4):764-71.

55. Nikooyeh B, Neyestani TR, Tayebinejad N, Alavi-Majd H, Shariatzadeh N, Kalayi A, et al. Daily intake of vitamin D- or calcium-vitamin D-fortified Persian yogurt drink (doogh) attenuates diabetes-induced oxidative stress: evidence for antioxidative properties of vitamin D. Journal of human nutrition and dietetics : the official journal of the British Dietetic Association. 2014;27 Suppl 2:276-83.

56. Paolisso G, Tagliamonte MR, Barbieri M, Zito GA, Gambardella A, Varricchio G, et al. Chronic vitamin E administration improves brachial reactivity and increases intracellular magnesium concentration in type II diabetic patients. The Journal of clinical endocrinology and metabolism. 2000;85(1):109-15.

57. Park S, Choi SB. Effects of alpha-tocopherol supplementation and continuous subcutaneous insulin infusion on oxidative stress in Korean patients with type 2 diabetes. The American journal of clinical nutrition. 2002;75(4):728-33.

58. Reaven PD, Herold DA, Barnett J, Edelman S. Effects of Vitamin E on susceptibility of low-density lipoprotein and low-density lipoprotein subfractions to oxidation and on protein glycation in NIDDM. Diabetes care. 1995;18(6):807-16.

59. Shab-Bidar SN, T. R.; Djazayery, A. The interactive effect of improvement of vitamin D status and VDR FokI variants on oxidative stress in type 2 diabetic subjects: a randomized controlled trial. European journal of clinical nutrition. 2015;69(2):216-22.

60. Sugden JA, Davies JI, Witham MD, Morris AD, Struthers AD. Vitamin D improves endothelial function in patients with Type 2 diabetes mellitus and low vitamin D levels. Diabetic medicine : a journal of the British Diabetic Association. 2008;25(3):320-5.

61. Tessier DM, Khalil A, Trottier L, Fulop T. Effects of vitamin C supplementation on antioxidants and lipid peroxidation markers in elderly subjects with type 2 diabetes. Archives of gerontology and geriatrics. 2009;48(1):67-72.

62. Vafa MH, N.; Moslehi, N.; Eghtesadi, S.; Heydari, I. Effect of tocotrienols enriched canola oil on glycemic control and oxidative status in patients with type 2 diabetes mellitus: A randomized double-blind placebo-controlled clinical trial. Journal of Research in Medical Sciences. 2015;20(6):540-7.

63. Winterbone MS, Sampson MJ, Saha S, Hughes JC, Hughes DA. Pro-oxidant effect of alpha-tocopherol in patients with type 2 diabetes after an oral glucose tolerance test--a randomised controlled trial. Cardiovascular diabetology. 2007;6:8.

64. Witham MD, Dove FJ, Dryburgh M, Sugden JA, Morris AD, Struthers AD. The effect of different doses of vitamin D(3) on markers of vascular health in patients with type 2 diabetes: a randomised controlled trial. Diabetologia. 2010;53(10):2112-9.

65. Wu JH, Ward NC, Indrawan AP, Almeida CA, Hodgson JM, Proudfoot JM, et al. Effects of alpha-tocopherol and mixed tocopherol supplementation on markers of oxidative stress and inflammation in type 2 diabetes. Clinical chemistry. 2007;53(3):511-9.

66. Yiu YF, Yiu KH, Siu CW, Chan YH, Li SW, Wong LY, et al. Randomized controlled trial of vitamin D supplement on endothelial function in patients with type 2 diabetes. Atherosclerosis. 2013;227(1):140-6.

67. Andersson A, Jonasson T, Ohlin H, Lindgren A, Hultberg B. Vitamin supplementation normalizes total plasma homocysteine concentration but not plasma homocysteine redox status in patients with acute coronary syndromes and hyperhomocysteinemia. Clinical chemistry and laboratory medicine. 2002;40(6):554-8.

68. Tonin FS, Steimbach LM, Wiens A, Perlin CM, Pontarolo R. Impact of Natural Juice Consumption on Plasma Antioxidant Status: A Systematic Review and Meta-Analysis. Molecules. 2015;20(12):22146-56.

69. Valdes-Ramos R, Guadarrama-Lopez AL, Martinez-Carrillo BE, Benitez-Arciniega AD. Vitamins and type 2 diabetes mellitus. Endocrine, metabolic & immune disorders drug targets. 2015;15(1):54-63.

70. Mahreen R, Mohsin M, Nasreen Z, Siraj M, Ishaq M. Significantly increased levels of serum malonaldehyde in type 2 diabetics with myocardial infarction. International journal of diabetes in developing countries. 2010;30(1):49-51.

71. Rani AJ, Mythili SV. Study on total antioxidant status in relation to oxidative stress in type 2 diabetes mellitus. Journal of clinical and diagnostic research : JCDR. 2014;8(3):108-10.

72. Matough FA, Budin SB, Hamid ZA, Alwahaibi N, Mohamed J. The role of oxidative stress and antioxidants in diabetic complications. Sultan Qaboos University medical journal. 2012;12(1):5-18.

73. Khodaeian M, Tabatabaei-Malazy O, Qorbani M, Farzadfar F, Amini P, Larijani B. Effect of vitamins C and E on insulin resistance in diabetes: a meta-analysis study. European journal of clinical investigation. 2015;45(11):1161-74.

74. Rafighi ZS, A.; Arab, S.; Mohd Yousof, R. Association of dietary vitamin C and e intake and antioxidant enzymes in type 2 diabetes mellitus patients. Glob J Health Sci. 2013;5(3):183-7.

75. von Hurst PR, Stonehouse W, Coad J. Vitamin D supplementation reduces insulin resistance in South Asian women living in New Zealand who are insulin resistant and vitamin D deficient - a randomised, placebo-controlled trial. The British journal of nutrition. 2010;103(4):549-55.

76. Church TS, Earnest CP, Wood KA, Kampert JB. Reduction of C-reactive protein levels through use of a multivitamin. The American journal of medicine. 2003;115(9):702-7.

77. Beveridge LA, Struthers AD, Khan F, Jorde R, Scragg R, Macdonald HM, et al. Effect of Vitamin D Supplementation on Blood Pressure: A Systematic Review and Meta-analysis Incorporating Individual Patient Data. JAMA internal medicine. 2015;175(5):745-54.

78. Lindstrom J, Ilanne-Parikka P, Peltonen M, Aunola S, Eriksson JG, Hemio K, et al. Sustained reduction in the incidence of type 2 diabetes by lifestyle intervention: follow-up of the Finnish Diabetes Prevention Study. Lancet. 2006;368(9548):1673-9.

79. Krul-Poel YH, Ter Wee M, Lips P, Simsek S. MANAGEMENT OF ENDOCRINE DISEASE: The effect of vitamin D supplementation on glycaemic control in patients with Type 2 Diabetes Mellitus: a systematic review and meta-analysis. European journal of endocrinology / European Federation of Endocrine Societies. 2016.

80. Colditz GA, Miller JN, Mosteller F. How study design affects outcomes in comparisons of therapy. I: Medical. Statistics in medicine. 1989;8(4):441-54.

81. Holman L, Head ML, Lanfear R, Jennions MD. Evidence of Experimental Bias in the Life Sciences: Why We Need Blind Data Recording. PLoS biology. 2015;13(7):e1002190.

82. Liu RH. Dietary bioactive compounds and their health implications. Journal of food science. 2013;78 Suppl 1:A18-25.

83. Huang D, Ou B, Prior RL. The chemistry behind antioxidant capacity assays. Journal of agricultural and food chemistry. 2005;53(6):1841-56.

84. Garcia-Cardenas V, Armour C, Benrimoj SI, Martinez-Martinez F, Rotta I, Fernandez-Llimos F. Pharmacists' interventions on clinical asthma outcomes: a systematic review. Eur Respir J. 2015.

85. Jones CW, Keil LG, Holland WC, Caughey MC, Platts-Mills TF. Comparison of registered and published outcomes in randomized controlled trials: a systematic review. BMC Med. 2015;13:282.

ÍNDICE REMISSIVO

S

T

U

V

www.atenaeditora.com.br
contato@atenaeditora.com.br
@atenaeditora
www.facebook.com/atenaeditora.com.br

CIÊNCIAS FARMACÊUTICAS:

Prevenção, promoção, proteção e recuperação da saúde

Atena Editora
Ano 2022

www.atenaeditora.com.br
contato@atenaeditora.com.br
@atenaeditora
www.facebook.com/atenaeditora.com.br

CIÊNCIAS FARMACÊUTICAS:

Prevenção, promoção, proteção e recuperação da saúde

Atena Editora
Ano 2022