

Association between serum Vitamin E concentrations and the presence of Metabolic Syndrome: A population-based cohort study

Maral Barzegar-Amini^{1,8,*}, Fateme khorramruz^{2,*}, Hamideh Ghazizadeh^{2,3,*}, Reza Sahebi³, Maryam Mohammadi-Bajgiran³, Hossein Mohaddes Ardabili⁴, Maryam Tayefi⁵, Susan Darroudi³, Mohsen Moohebaty¹, Alireza Heidari-Bakavoli¹, Akram Mohammadi¹, Hamid Reza Sadeghnia⁶, Gordon A. Ferns⁷, Seyed-Javad Hoseini⁶, Majid Ghayour-Mobarhan³

¹Cardiovascular Division, Vascular Surgery Research Center, Mashhad University of Medical Sciences, Mashhad, Iran; ²Student Research Committee, Biochemistry of Nutrition Research Center, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran; ³International UNESCO Center for Health Related Basic Sciences and Human Nutrition, Mashhad University of Medical Sciences, Mashhad, Iran; ⁴Student Research Committee, Department of New Science and Technologies, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran; Norwegian Center for e-health Research, University hospital of North Norway, Tromsø, Norway; ⁵Department of Medical Biotechnology, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran; ⁷Brighton & Sussex Medical School, Division of Medical Education, Falmer, Brighton, Sussex BN1 9PH, UK; ⁸Allergy Research Center, Mashhad University of Medical Sciences, Mashhad, Iran. *M BA, F KH and H GH Equally contributed as first author

Abstract. *Background.* Metabolic syndrome (MetS) is a cluster of clinical and metabolic features that include central obesity, dyslipidemia, hypertension and impaired glucose tolerance. These features are accompanied by increased oxidative stress and impaired antioxidant defenses. Vitamin E is a major factor in the non-enzymatic antioxidant defenses. The aim of present study was to investigate the association between serum levels of vitamin E and the presence of MetS and its components in a subsample population of Mashhad stroke and heart atherosclerotic disorder (MASHAD) study. *Methods.* This cross-sectional study was carried out in 128 subjects with MetS and 235 subjects without MetS. MetS was defined according to the International-Diabetes-Federation criteria. Serum levels of vitamin E were measured using the HPLC method. Anthropometric and biochemical parameters were measured using standard protocols. *Results.* MetS patients had significantly lower serum levels of vitamin E (Vit E), Vit E/Total cholesterol (TC), and Vit E/ (TC+triglyceride(TG)) compared to the control group ($P < 0.05$). Vit E/ (TG+TC) was also significantly lower in diabetics or those with elevated levels of highly sensitive C-reactive protein (hs-CRP). Additionally, there was a significant association between Vit E/ (TG + TC) and MetS (OR:0.87, 95% CI (0.78-0.96)). *Conclusions.* There is a significant inverse association between Vit E/ (TG + Total Cho) and the presence of MetS. Moreover, a significantly lower Vit E/ (TC+TG) was observed in subjects with more than 3 components of the MetS. The evaluation of this association in a larger population may help further confirm these findings.

Keywords: metabolic syndrome; vitamin E; oxidative stress; antioxidant vitamins.

Abbreviation

Metabolic syndrome: MetS; Mashhad stroke and heart atherosclerotic disorder: MASHAD; High pressure liquid chromatography: HPLC; Vit: Vitamin; Total

cholesterol: TC; TG: Triglycerides; Fasting blood glucose: FPG; High sensitive C-reactive protein: hs-CRP; Reactive oxygen species: ROS; Systolic blood pressure: SBP; Diastolic blood pressure: DBP; Low density lipoprotein: LDL; High density lipoprotein: HDL; Na-

tional Cholesterol Education Program: NCEP; Adult treatment panel: ATP; International Diabetes Federation: IDF; Body mass index: BMI; Analysis of Variance: ANOVA; Hypertension: HTN; SD: standard deviation; Q: Quartile; Cardiovascular disease: CVD

Introduction

Metabolic syndrome (MetS) is a cluster of metabolic abnormalities including central obesity, dyslipidemia, hypertension (HTN) and impaired glucose tolerance. It is associated with an increased risk of obesity, diabetes mellitus and cardiovascular disease (CVD) (1, 2). Several environmental and genetic factors are involved in the pathogenesis of MetS. Furthermore, increased oxidative stress has a critical role in the etiology of complications associated with MetS and may lead to the impaired angiogenesis, endothelial dysfunction and a proinflammatory and prothrombotic state in vasculature (3, 4). Oxidative stress results from an imbalance between the synthesis of reactive oxygen species (ROS) and their removal by the antioxidant defense system, as well as dietary antioxidants (e.g. beta-carotene, vitamin E, and selenium) (5).

Vitamin E comprise two major subgroup: tocopherol and tocotrienols, that each have four different isomers (α , β , γ , and δ). α -tocopherol forms over 90% of the total tocopherols in plasma (6, 7). (6) Whilst dietary vitamin E is rich in γ -tocopherol, the major form in the plasma is α -tocopherol which is associated with several biological activities (8). Regarding the importance of fat-soluble biological antioxidant in the body, vitamin E has a significant defensive role against oxidative stress and lipid peroxidation as well as hepatic inflammation and, therefore, preventing pathological conditions which include chronic diseases such as cardiovascular disease, diabetes mellitus and cancer (9-11).

A limited number of studies have investigated the relationship between vitamin E levels and MetS, but the results have been inconsistent. Vitamin E has been proposed as a potential agent for attenuating MetS and its components. Vitamin E is also reported to have anti-obesity, anti hypercholesterolemic, anti-diabetic and anti-hypertensive properties (12-16). It is also suggested that Vitamin E could improve inflam-

matory status, insulin resistance, blood glucose as well as dyslipidemia. However Godala et al concluded that Vit E levels were not associated with systolic blood pressure (SBP), total cholesterol, low density lipoprotein (LDL) and triglycerides (12, 17). There are several other studies in which no association between vitamin E and MetS have been found (18-21).

Since patients with MetS have high levels of oxidative stress and impaired antioxidant defenses, also there is controversial evidence about whether antioxidants can attenuate the progression of MetS, so in the present study we aimed to investigate the association of Vitamin E with MetS and its component.

Material and Methods

Study Population

The present study population comprised 128 subjects with MetS and 235 healthy subjects without MetS. Participants were adults aged 35-65 years, and were randomly selected from Mashhad stroke and heart atherosclerotic disorder (MASHAD) study, 2010-2020 (22). The exclusion criteria were as follows: presence of any systemic diseases such as autoimmune diseases, taking medications that included: lipid-lowering and/or anti-diabetic drugs, and being pregnant or lactating. Written informed consent was obtained from eligible subjects who wished to participate in the study. This study was approved by the Medical Ethics Committee of Mashhad Medical Sciences University.

Definition of Metabolic Syndrome

In accordance with the International Diabetes Federation (IDF) criteria, MetS was defined as having central obesity (defined as waist circumference of ≥ 94 cm for male or ≥ 80 cm for female) plus any two of the following four factors:

1. Elevated TG: ≥ 150 mg/dL (1.7 mmol/L) or specific treatment for this lipid abnormality.
2. Low HDL-cholesterol: < 40 mg/dL (1.03 mmol/L) in males and < 50 mg/dL (1.29 mmol/L) in females or specific treatment for dyslipidemia.
3. Elevated systolic blood pressure (SBP) ≥ 130 or di-

- astolic blood pressure (DBP) ≥ 85 mm Hg; (FPG) ≥ 100 mg/dL (5.6 mmol/L) or treatment of previously diagnosed hypertension.
4. Elevated fasting blood glucose: (FBG) ≥ 100 mg/dL (5.6 mmol/L) or previously diagnosed type 2 diabetes (22)(61).

Anthropometric and Biochemical Measurements

Anthropometric parameters (weight, height, waist and hip circumference) were measured using standard procedures. Body mass index (BMI) was calculated as the ratio of weight (kg) to height in square meters (m²) and BMI of 20–24.9, 25–29.9 and ≥ 30 kg/m² were considered as normal, over-weight and obese, respectively. The mean values of three times measurement of systolic and diastolic pressure with a 30-minute interval was recorded as blood pressure by using a standardized mercury sphygmomanometer. Fasting venous blood samples (10 mL) were collected in vacuum tubes by an expert phlebotomist after 12–14 hours overnight fasting. The serum concentration of fasting blood glucose, total cholesterol, HDL, low density lipoprotein (LDL) and TG were assessed enzymatically using commercial kits as described previously (23, 24).

Serum Vitamin E Measurement

Serum levels of vitamin E (α -tocopherol) were measured by HPLC using a modified method of Papas et al.(25, 26). Since Vitamin E as a fat-soluble vitamin is circulated in blood stream by lipoproteins, in order to normalize serum concentration of Vit E and correct vitamin-free lipoproteins, measured Vit E divided to total cholesterol and total cholesterol + TG(27, 28). {Thurnham, 1986 #161;Barzegar-Amini, 2019 #82}

Statistical analyses

All statistical analyses were performed using SPSS version 20.0 (SPSS Inc. Chicago, IL, USA). The normal distribution was determined using the Kolmogorov-Smirnov test. Based on normality, comparison of 2 independent groups were performed using t-tests or Mann-Whitney U tests and Analysis of Variance (ANOVA) and Kruskal-Wallis tests were

used to compare the values among more than 2 groups. Although Bonferroni post hoc correction was assessed to determine statistical differences between healthy subjects and different combination of components of MetS. The data were expressed as mean \pm SD, and median (IQR) for normally and non-normally distributed variables, respectively. Logistic regression was used to assess the relationship between Vit E indices with MetS and its components. A *p*-value < 0.05 was considered statistically significant.

Results

General characteristics of the subjects

Clinical and demographic features of participants are listed in Table 1. A total of 363 subjects, including 47% men and 53% women were recruited into this cross-sectional study. The mean value of BMI, height, weight, hip circumference, HDL, Total Cholesterol, hs.CRP and uric acid had a significant difference between male and female groups.

Levels of Vit E indices in subjects with risk factors of CVD

The serum levels of Vit E, Vit E/ TC and Vit E/ (TG + TC) were lower in subjects with more than 3 components of MetS compared to subjects without component (i.e. without MetS) or with 1 and/or 2 components (Table 2) while this difference was alone significant for Vit E/TC+TG. We then assessed the levels of Vit E, Vit E/ TC and Vit E/ (TG + TC) in subjects with risk factors of CVD (Table 3). Subjects with diabetes had lower levels of Vit E/ (TG + TC) than subjects without diabetes (*P*= 0.03). Moreover, there was a negative significant association between Vit E/ (TG + TC) and hs-CRP (*P*<0.05). Accordingly, neither Vit E nor Vit E/ TC had significant differences in patients with other risk factors of CVD compared with the control group (Table3).

Association of Vit E indices with Mets

Based on Table 4 subjects with MetS had significantly lower Vit E, Vit E/ TC and Vit E/ (TG +

Table 1. Baseline characteristics of the study subjects according to sex

Variable	Male (n=173)	Female (n=190)	P-value
Waist circumference (cm)	93.12±9.74	96.51±12.84	0.005
BMI	25.83±4.04	28.91±4.63	<0.001**
Hip circumference (cm)	101.08±7.79	105.69±9.72	<0.001**
HDL (mg/dl)	39.08±9.57	45.33±10.09	<0.001**
Total Cholesterol (mg/dl)	185.14±46.63	195.23±44.53	0.037*
Triglycerides (mg/dl)	118.5(82.75-166)	109.00(80-157)	0.327
LDL (mg/dl)	113.18±33.79	119.91±38.33	0.079
FBG (mg/dl)	93.46±41.77	91.49±42.01	0.657
Systolic Blood Pressure (mmhg)	120.75±16.43	120.70±20.45	0.980
Diastolic Blood Pressure (mmhg)	79.02±10.14	78.16±11.89	0.461
Serum -Tocopherol (µg/dL)	3.11 (14.38)	3.11 (11.93)	0.983
hs-CRP(g/dl)	1.56(0.84-3.18)	2.02 (1.12-3.6)	0.029*
Uric Acid (mg/dl)	5.39±1.66	4.14±1.13	<0.001**
Vit E/ Total Cho (µmol/mmol)	0.02(0.007-0.14)	0.03(0.006-0.14)	0.59
Vit E/ Total Cho + TG (µmol/mmol)	0.02(0.005-0.1)	0.02(0.004-0.1)	0.86

Values are expressed as mean±SD, median and interquartile range for normally and non-normally distributed variables, respectively. HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein; cholesterol; FBG: fasting blood glucose; BMI: Body Mass Index; Cho, Cholesterol; TG, Triglyceride. * P value<0.05 and ** P value<0.001

Table 2. Levels of Vitamin E, Vit E/Total Cho, Vit E/ (TG + Total Cho) and Total Cholesterol in subjects with the different numbers of the metabolic syndrome features

Variable	Number of metabolic syndrome components			P-value
	Zero component	One or Two components	More than Three components	
Vit E(µg/dL)	3.11 (11.27)	3.11 (20.53)	2.11 (5.14)	0.23
Vit E/TC(µmol/mmol)	0.08 (0.35)	0.09 (0.47)	0.04 (0.17)	0.12
Vit E/TC+TG(µmol/mmol)	0.04 (0.21)	0.05 (0.32)	0.02 (0.10)	0.01
Total Cholesterol (mg/dL)	197.68 (37.84) ^a	186.33 (36.56)	198 (39.27) ^b	<0.001

Values are presented as median (IQR) and mean±SD. TC, Total Cholesterol; TG, Triglyceride. Kruskal-wallis test was used. a and b show significant difference between one and two component groups with zero and More than Three components, respectively.

TC) in comparison to subjects without MetS (<0.05). Association of Vit E indices with Mets showed that by increasing 0.1 unit of serum Vit E/ (TG + TC) there was a significant decrease 13% in risk of MetS, based on univariate and multivariate regression models (OR:0.87, 95% CI (0.79-0.97) and OR:0.87, 95% CI (0.78-0.96), respectively) (P <0.05).

Discussion

The results of the present study showed that subjects with MetS had significantly lower serum levels of all Vit E

indices including Vit E, Vit E/TC, and Vit E/(TC+TG). According to the global thresholds all our population were Vit E deficient. Moreover, we showed a negative association between the levels of Vit E/ (TG+TC) and severity of MetS according number of criteria presented. We showed Vit E/ (TG+TC) was significantly associated with high risk of MetS, elevated hs-CRP and FBS serum levels. In the recent study we showed Vit E was significantly lower in individuals with dyslipidemics (22).

In our population, the median serum α -tocopherol was 3.11 (14.38) µg/dL and 3.11 (11.93) µg/dL in male and female subjects, respectively. While it was similar to the results of Ghaffari et al. accordingly mean of se-

Table 3. Levels of Vit E, Vit E/Total Cho, Vit E/(TG+Total Cho) in subjects with risk factors of CVD

Variable		Vitamin E ($\mu\text{g/dL}$)	Vit E/ TC ($\mu\text{mol/mmol}$)	Vit E/ (TC+TG) ($\mu\text{mol/mmol}$)
Waist Circumferences	Normal	3.11 (20.53)	0.03(0.006-0.14)	0.03(0.005-0.12)
	M:W.C \geq 94 cm F: W.C \geq 80 cm	3.11 (8.05)	0.03(0.006-0.13)	0.02(0.005-0.1)
	P-value	0.88	0.83	0.52
Diabetes	Normal	3.11 (14.30)	0.03(0.007-0.14)	0.02(0.005-0.11)
	FBS \geq 110 (mg/dl) or diabetic history	2.13 (11.57)	0.01(0.005-0.08)	0.009(0.004-0.05)
	P-value	0.25	0.10	0.04*
Hypertension	Normal	3.11 (13.56)	0.03(0.006-0.12)	0.02(0.005-0.1)
	SBP \geq 135 or DBP \geq 85 (mmHg)	3.11 (14.16)	0.02(0.006-0.17)	0.02(0.004-0.11)
	P-value	0.90	0.98	0.8
BMI (Kg/m ²)	Normal	3.11 (20.53)	0.03(0.007-0.18)	0.03(0.005-0.14)
	Overweight	3.11 (7.46)	0.03(0.007-0.09)	0.02(0.005-0.06)
	Obesity	3.11 (10.48)	0.02(0.005-0.13)	0.02(0.004-0.08)
	P-value	0.42	0.35	0.13
hs-CRP (g/dl)	\leq 1	4.59 (20.42)	0.04(0.008-0.17)	0.03(0.006-0.14)
	(1-3)	3.11 (10.24)	0.03(0.006-0.11)	0.02(0.004-0.09)
	\geq 3	3.11 (10.29)	0.02(0.006-0.1)	0.01(0.004-0.08)
	P-value	0.16	0.08	0.04*

Data were expressed as Median (Q1-Q3). BMI, Body Mass Index; hs-CRP, High-sensitivity C-reactive protein; M, Male; F, Female; FBS, Fasting Blood Sugar; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure. Kruskal-Wallis Test.

Table 4. Association between serum Vit E indices and metabolic syndrome

Variables	(Median (IQR))			Model 1		Model 2	
	Yes (n;128)	No (n;235)	p-value	OR (CI 95%)	p-value	OR (CI 95%)	p-value
Metabolic syndrome							
Vitamin E($\mu\text{g/dL}$)	3.10 (5.68)	3.11 (18.83)	*0.037	0.86 (0.68-1.09)	0.23	0.84 (0.66-1.06)	0.15
Vit E/TC ($\mu\text{mol/mmol}$)	0.02 (0.07)	0.03 (0.16)	*0.016	0.96 (0.91-1.01)	0.11	0.95 (0.90-1.01)	0.08
Vit E/(TG + TC) ($\mu\text{mol/mmol}$)	0.01 (0.05)	0.03 (0.13)	**<0.001	0.87 (0.79-0.97)	0.01	0.87 (0.78-0.96)	<0.001

Values are expressed as Median (IQR) for non-normally distributed variables. Logistic regression was used to evaluate the Association between serum Vit E indices and Met. Model 1 presented before adjusting for confounder factors and model 2 presented after adjusting for confounder factors (sex, age and smoking).

rum concentration of vitamin D was 4.5 $\mu\text{g/dL}$ in the control group (29), Korea (reports vary from 15.14 to 44.95 $\mu\text{mol/L}$) (30), US (males: 26.86 (26.03, 27.73) and females: 27.88 (27.09, 28.70) $\mu\text{mol/L}$) (31), and even in Iran (ranging from 16.16 to 159.96 $\mu\text{mol/L}$ reported in studies from different Iranian cities) (32-34). Our previous studies also proved such a low level of Vit E serum concentration in Mashhad (35, 36) but not in Surrey, UK (37). Although sex, age, and ethnicity have shown significant association with α -tocopherol levels (31), so it maybe useful to explain such a difference between our results and the others.

As a fat soluble vitamin, we should adjust Vit E values according to simultaneous lipid profile in order to have a more comprehensive insight about its adequacy and determine a common reliable threshold for this vital vitamin. There are a number of different methods for such adjustment (38-40), but in order to have more universal index for inter-literature comparisons, it is suggested to simply calculate Vit E/TC and Vit E/(TC+TG) ratios (31). Above reported great differences in plasma Vit E are also seen in our calculated ratios having 11.6 $\mu\text{mol/L}$ (41), 2.22 $\mu\text{mol/mmol}$ (42), and 1.59 $\mu\text{mol/mmol}$ (42) as inadequacy threshold for

Vit E, Vit E/TC and Vit E/(TC+TG) respectively, all our cases were deficient in Vit E. This brings up the need for further mass population epidemiologic studies with needed adjustments in this region to find out the reason for such a great gap in Vit E values.

In our study all three Vit E indices (Vit E, Vit E/TC and Vit E/ (TC+TG)) were significantly lower in MetS+ subjects. This is partly in line with a previous study done by Godala et al. in which they found lower levels of serum Vit E in MetS+ cases. Palmieri et al. also reported a similar result in regard with α -tocopherol (43). Similarly Sempértegui et al. showed a strong inverse correlation between plasma Vit E and MetS risk (44).

Increased oxidative stress in the context of MetS (due to inflammation, obesity, hyperglycemia, hypertension, and dyslipidemia) and therefore increased activity of antioxidants such as Vit E and therefore depleting its internal and external sources can explain such a finding (17, 46)(62). According to the role of adipose tissue in storing fat-soluble vitamins, the other probable theory is shifting more amount of Vit E from plasma to adipose tissue in MetS patients in whom obesity is a major component (17, 45). Another theory in regard with lower Vit E values is the impairments in both intestinal absorption of Vit E and hepatic functions caused by accompanying inflammation and oxidative stress in MetS (46).

In contrary, a number of previous studies showed different findings. In Taiwan, Yen et al. showed significantly higher plasma α -tocopherol levels in MetS+ cases, but no significant differences in Vit E/TG ratios. They reported higher levels of TG in MetS+ cases, that was suggested high TG is a reason for higher Vit E levels in MetS+ cases, a theory which may well explain non-significant difference in Vit E/TG ratios (47). To support their finding, they have also provided dietary results in which MetS+ cases had significantly higher intake of Vit E that did not remain significant after normalizing for their fat intake (48). Higher Vit E in MetS may also be the outcome of increased need for antioxidant defense against MetS+ components. Some studies reported higher levels of Vit E concentrations in MetS+ subjects, a relationship which did not remain significant after adjusting Vit E values for TG and cholesterol; such a finding can be explained

by the apparently higher levels TG and TC in MetS cases (47, 49).

A recent and interesting study that measured α -tocopherol catabolites in urine proposed another explanation for higher Vit E concentrations in MetS+ patients; higher levels of plasma lipids in MetS cases contributes to the slower α -tocopherol turnover and therefore an unreal higher Vit E measures in plasma (50).

Results from The Third National Health and Nutrition Examination Survey (NHANES) are also notable in which despite lower levels of several antioxidants, both Vit E and Vit E/TC levels were significantly higher in MetS+ group (51). After adjusting the data for intake of vitamins, minerals, fruits, and vegetables the results completely reversed and showed a significantly lower levels of Vit E in MetS+ subject. Serum Vit E was positively associated with MetS in NHANES study, an association which remained significant but became negative after adjusting for TG and cholesterol levels (51). Similar to our results, it can be explained by increasing antioxidant turn over in the context of oxidative condition of MetS.

One probable factor that may affect plasma levels of Vit E is dietary intake. Although Al-Daghri et al. observed significantly lower dietary intake of Vit E in MetS+ cases (52), it is not a consistent finding in all studies; for example, Wei et al. and beydoun et al. both found no associations between Vit E intake and MetS that were similar to our findings (49, 53).

After grouping the subjects according to the number of MetS criteria they have and studying Vit E indices in each group, we showed a significantly decreasing trend only in Vit E/(TC+TG) amounts, in other words, Vit E/(TC+TG) was negatively associated with the number of MetS criteria (table 3). Other similar investigations did not show consistent results. Ford et al. reported a significant positive association between both Vit E and Vit E/TC values and the number of MetS criteria (51). Beydoun et al. also in a dose-response model, showed a direct relationship between Vit E levels and MetS criteria count (54)

Analyzing the serum concentrations Vit E indices in cases with or without MetS risk factors including Waist Circumferences, Diabetes, Hypertension, Dyslipidemia, BMI, and hs-CRP only Vit E/(TC+TG)

was significantly different between groups; in other words, diabetics, and cases with elevated hs.CRP values had significantly lower Vit E/(TC+TG) ratios. Beydoun et al. found a significant positive association between Vit E and Hypertriglyceridemia but not low HDL-c, high blood pressure, Hyperglycemia, abdominal obesity, and elevated CRP (54). Faure et al. showed a significant association between Vit E and both serum cholesterol and triglycerides (55). In a study done by Garcia et al Vit E was positively associated with BMI only before adjusting for lipids (56). Contrary to this, Wallström et al. despite reporting a significant association between Vit E and central adiposity parameters (waist circumference and waist-to-hip ratio), could not show a generalized association between Vit E and BMI (57). There are not a common consensus in regard with Vit E anthropometric and biochemical associations yet (58).

Conclusion

To our knowledge this is the first study that investigates the association of Vit E, Vit E/TC, and Vit E/(TC+TG) levels with independent and accumulative MetS criteria in this region. Besides finding a great gap between Vit E concentration in our subjects and global thresholds (nearly all our cases were Vit E deficient), we showed a significant inverse association between all Vit E indices and metabolic syndrome. Moreover a significant decline in Vit E/ (TC+TG) was observed in subjects with more than 3 components of the MetS. These brings up the need for more comprehensive clinical trials to examine the effectively of Vit E supplementation in prophylaxis and treatment of MetS especially in Vit E-deficient populations and societies with high prevalence of MetS. Previous studies (59) have been done on societies with less Vit E inadequacy but there are still a gap for such studies in developing countries with high Vit E deficiency rates.

Acknowledgements: We would like to thank Mashhad University of Medical Sciences Research Council for financial supports

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, eq-

uity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

Ethics approval and consent to participate

The approval number from the constituted review board, the Ethics Committee of Mashhad University of Medical Sciences (MUMS) is IR.MUMS.MEDICAL.REC.1386.250.

Availability of data and materials: Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

Funding: This work was supported by a grant (Majid Ghayour Mobarhan) from Mashhad University of Medical Science (MUMS), Iran.

Authors' Contributions: We declare that the Authors contributed significantly towards the research study i.e., (a) conception, design and/or analysis and interpretation of data and to (b) drafting the article or revising it critically for important intellectual content and on (c) final approval of the version to be published.

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Received: 14 January 2020

Accepted: 1 February 2020

Correspondence:

Majid Ghayour-Mobarhan, MD, PhD

Metabolic Syndrome Research Center, Mashhad University of Medical Sciences, Mashhad, Iran.

Tel:+985138002288

Fax: +985138002287

Email: ghayourm@mums.ac.ir

Seyed javad Hoseini, MD, PhD

Department of Medical Biotechnology, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

Email: hoseinij1@mums.ac.ir