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Research Article

Oral Supplementation of Vitamin C Reduced Lipid Peroxidation and Insulin Resistance in Patients with Type 2 Diabetes Mellitus

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ABSTRACT
We performed a randomized, double blind, placebo controlled trial to investigate the effect of vitamin C (VitC) supplementation on lipid peroxidation, total antioxidant capacity (TAC), insulin levels and insulin resistance in 50 patients with type 2 diabetes mellitus (T2DM) and 50 T2DM patients were the placebo group. All T2DM patients received either VitC or placebo identical tablet daily for 60 days study period. At the end of the study, the median of MDA, a marker of lipid peroxidation, insulin levels and insulin resistance were significantly decreased (p<0.005) while TAC and insulin sensitivity were significantly increased (p<0.005) with in the VitC supplementation group. These effects also cause the reduction on blood glucose, HbA1c, triglycerides and increasing HDL-C levels. Vitamin C supplementation could be considered as an additional dietary supplement option to prevent and regulate underlying diabetic complications.

Keywords: Type 2 diabetes mellitus, Vitamin C, oxidative stress, total antioxidant, insulin resistance

INTRODUCTION

Ascorbic acid or vitamin C (VitC) is an important antioxidant in human circulation[1]. It plays an important role in the protection from reactive oxygen species (ROS) and reactive nitrogen species (RNS) by scavenging oxygen-derived free radicals[2]. It has been demonstrated that basal VitC reduction[3,4] and also increased oxidative stress in type 2 diabetes mellitus (T2DM) patients[2,5,6]. Vitamin C can cause many chemical reactions like glucose thus it is effective to prevent non-enzymatic protein glycosylation[7]. Increased oxidative stress appears to be a deleterious factor leading to insulin resistance, dyslipidemia, impaired glucose tolerance and hyperglycemia[8].

Most T2DM patients have lipid metabolism disorders such as lipid triad, associated with dyslipidemia[9]. Lipid triad comprises with hypertriglyceridemia, low levels of high-density lipoprotein cholesterol (HDL-C) and the appearance of small, dense, low density lipoprotein[10,11]. Ness et. al.[12] demonstrated the beneficial effects of VitC on lipids in human. Sargeant et. al.[13] also demonstrated the inverse relationship between glycosylated hemoglobin (HbA1c) and plasma vitamin C levels. Therefore, our present study was designed to evaluate the effects of a sixty days supplementation with VitC on insulin levels, insulin resistance, lipid peroxidation and total antioxidant capacity in patients with T2DM.

MATERIAL AND METHODS

Subjects: One hundred patients with T2DM participated in a randomized, double-blind, placebo-controlled trial, 60-days study approved by the Ethics Committee of the Naresuan University (55-03-01-0020). The randomization of these patients was done by using a table of random numbers with block of four to receive VitC or placebo. The treatment code was concealed by placing the patient's assignments in sequence in sealed opaque envelopes that were drawn in ascending consecutive order. The codes were kept strictly confidential for blinding the researchers and subjects those were broken at the end of the study. These patients were randomly selected from a volunteer list who previously had attended the Diabetes Care Clinic activities of the Ladyao Hospital, Nakornsawan Province (December 2012-December 2013). These patients have been diagnosed or received medications as T2DM over 5 years, aged ≥40 years old, no acute cardiovascular or neurologic event in the prior 6 months, no history of active tobacco smoking and no oral intake of vitamin supplements in the last 4 weeks and the medical treatment for diabetes had to be stable for the last 3 months as the inclusion criteria. The exclusion criteria were overt cardiovascular, neuromuscular, arthritic, pulmonary or other debilitating diseases and those who currently smoked or had poor glycemic control or were on insulin treatment. Medications were not altered in either group during the study period. The duration of diabetes was similar in both experimental and control groups: 7.0 (5.0-10.0) years for the VitC groups and 8.0 (6.0-10.0) years for the placebo

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Table 1: Comparison of baseline characteristic of vitamin C supplementation and placebo groups

Variables	Baseline VitC group (n=50)	Baseline placebo group (n=50)	*p*-value
Age (years)	57.5 (49.8-65.0) *	58.0 (50.5-64.0) *	0.748
Duration (years)	7.0 (5.0-10.0)	8.0 (6.0-10.0)	0.081
WC (cm)	90.5 (84.0-97.0)	95.0 (88.0-100.0)	0.063
BMI (kg/m^2)	25.4 (23.3-28.6)	25.6 (23.2-27.8)	0.757
Systolic BP (mmHg)	129.5 (120.0-137.3)	130.0 (121.0-140.0)	0.283
Diastolic BP (mmHg)	80.0 (76.0-90.0)	80.0 (73.5-90.0)	0.965
Glu (mg/dl)	156.0 (126.5-188.3)	138.0 (116.0-167.0)	0.046
TC (mg/dl)	174.0 (158.3-188.5)	170.0 (147.0-194.5)	0.555
TG (mg/dl)	148.5 (97.5-193.5)	124.0 (89.0-202.0)	0.633
HDL-C (mg/dl)	49.0 (40.0-54.5)	55.0 (44.5-65.0)	0.036
LDLc (mg/dl)	96.5 (76.8-108.3)	85.0 (69.0-105.5)	0.140
HbA1c (mmol/mol)	58.02 (51.55-68.92)	60.66 (56.29-68.31)	0.095
TG/HDLc ratio	2.97 (1.88-5.22)	2.39 (1.45-4.42)	<0.001
Insulin (pmol/l)	7.80 (3.78-10.98)	4.80 (3.70-7.80)	0.031
HOMA-IR	2.81 (1.19-4.85)	1.63 (1.14-3.05)	0.039
QUICK	0.339 (0.317-0.367)	0.347 (0.321-0.376)	0.392
MDA (µmol/l)	3.35 (2.86-5.35)	3.54 (2.99-5.72)	0.510
TAC (µmolTroloxEquiv/L)	4.39 (3.42-6.08)	3.70 (3.15-4.91)	0.059

* median (interquartile)

Table 2: Effect of vitamin C supplementation on insulin, QUICKI, MDA, and TAC in T2DM patients

Variables	Before Administration (n=50)	After Administration (n=50)	Difference (n=50)	*p*-value
Age (years)	57.5 (49.8-65.0)*	57.5 (49.8-65.0)*	-	-
Duration (years)	7.0 (5.0-10.0)	7.0 (5.0-10.0)	-	-
WC (cm)	90.5 (84.0-97.0)	92.0 (82.8-98.0)	0.0 (-3.00-1.25)*	0.266
BMI (kg/m^2)	25.4 (23.3-28.6)	25.4 (23.4-29.0)	-0.18 (-0.84-0.37)	0.017
Systolic BP (mmHg)	129.5 (120.0-137.3)	130.0 (120.8-140.3)	0.0 (-12.3-8.5)	0.299
Diastolic BP (mmHg)	80.0 (76.0-90.0)	78.5 (72.0-87.3)	1.0 (-6.3-7.3)	0.506
Glu (mg/dl)	156.0 (126.5-188.3)	124.5 (107.5-164.0)	21.0 (9.8-39.3)	<0.001
TC (mg/dl)	174.0 (158.3-188.5)	170.0 (156.5-192.8)	-2.5 (-19.3-19.0)	0.980
TG (mg/dl)	148.5 (97.5-193.5)	119.0 (69.3-156.8)	28.0 (2.0-54.0)	<0.001
HDL-C (mg/dl)	49.0 (40.0-54.5)	56.0 (44.0-65.3)	-7.0 (-13.0-(-2.8))	<0.001
LDLc (mg/dl)	96.5 (76.8-108.3)	90.0 (74.0-108.3)	1.5 (-11.5-15.3)	0.442
HbA1c (mmol/mol)	58.02 (51.55-68.92)	52.48 (49.52-58.58)	5.92 (2.77-9.06)	<0.001
TG/HDLc ratio	2.97 (1.88-5.22)	2.14 (1.21-3.10)	0.76 (0.26-2.17)	<0.001
Insulin (pmol/l)	7.80 (3.78-10.98)	5.25 (3.88-8.20)	1.60 (-0.30-3.13)	<0.001
HOMA-IR	2.81 (1.19-4.85)	1.82 (1.01-3.27)	0.84 (0.03-2.09)	<0.001
QUICK	0.339 (0.317-0.367)	0.348 (0.320-0.383)	-0.009 (-0.014-(-0.004)	<0.001
MDA (µmol/l)	3.35 (2.86-5.35)	3.21 (2.66-3.61)	0.44 (0.11-1.31)	<0.001
TAC (µmolTroloxEquiv/L)	4.39 (3.42-6.08)	4.73 (3.88-6.18)	-0.30 (-0.54-(-0.07))	<0.001

* median (interquartile)

group. The identical-looking capsules of VitC tablets and placebo tablets were purchased from the Government Pharmaceutical Organization, Thailand. After baseline assessment for eligibility, all patients were requested to take one VitC tablets (1000 mg) or placebo tablets before the bed times a day, every day for a total of 60 days. Patients were requested to take their conventional medication and record their randomized tablets in each day. One 24 h recall was conducted for each subject and especially elderly patients. Patients were advised to control their meals with low carbohydrate and low fat same as the physician suggestion. All patients were requested to return the day after completing their study period to assess the effect of the supplementation and provided written informed consent before participating and providing blood sample for their health check in this study.

Anthropometric and blood pressure measurement

Height, weight and blood pressure (BP) were measured and body mass index (BMI) was calculated. Waist circumference (WC) was measured at the midpoint between the both of rib cage and the top of lateral border of iliac crest during minimal respiration. BP was measured after the participants were seated and rested for 5 minutes as the mean value of at least two measurements of these participants on the same day with a Terumo digital blood pressure monitor (ES-P110).

Blood sample collection and biochemical determination

Table 3: Effect of placebo supplementation on insulin, QUICKI, MDA, and TAC in T2DM patients

Variables	Before Administration (n=50)	After Administration (n=50)	Difference (n=50)	*p*-value
Age (years)	58.0 (50.5-64.0) *	58.0 (50.5-64.0)*		
Duration (years)	8.0 (6.0-10.0)	8.0 (6.0-10.0)		
WC (cm)	95.0 (88.0-100.0)	95.0 (87.0-99.0)	-1.0 (-3.0-2.5)*	0.657
BMI (kg/m^2)	25.6 (23.2-27.8)	26.9 (22.9-28.5)	-0.45 (-0.91-0.00)	0.001
Systolic BP (mmHg)	130.0 (121.0-140.0)	135.0 (127.0-142.0)	-5.0 (-10.0-3.0)	0.007
Diastolic BP (mmHg)	80.0 (73.5-90.0)	83.0 (78.0-95.0)	-1.0 (-11.5-5.0)	0.044
Glu (mg/dl)	138.0 (116.0-167.0)	146.0 (116.0-191.0)	-9.0 (-29.0-9.5)	0.058
TC (mg/dl)	170.0 (147.0-194.5)	178.0 (157.0-205.5)	-11.0 (-26.5-10.0)	0.012
TG (mg/dl)	124.0 (89.0-202.0)	132.0 (92.5-176.5)	1.0 (-44.5-22.0)	0.937
HDL-C (mg/dl)	55.0 (44.5-65.0)	54.0 (45.0-65.0)	1.0 (-11.0-8.0)	0.549
LDLc (mg/dl)	85.0 (69.0-105.5)	84.0 (71.1-115.0)	1.8 (-17.0-15.5)	0.940
HbA1c (mmol/mol)	60.66 (56.29-68.31)	63.94 (59.57-73.78)	-4.37 (-8.75-1.64)	0.002
TG/HDLc ratio	2.39 (1.45-4.42)	2.04 (1.32-3.11)	0.14 (-0.62-1.21)	0.357
Insulin (pmol/l)	4.80 (3.70-7.80)	5.60 (3.60-8.50)	-0.20 (-2.05-1.45)	0.400
HOMA-IR	1.63 (1.14-3.05)	2.09 (1.12-3.15)	-0.20 (-0.99-0.43)	0.251
QUICK	0.347 (0.321-0.376)	0.341 (0.321-0.376)	0.004 (-0.004-0.011)	0.036
MDA (µmol/l)	3.54 (2.99-5.72)	4.42 (3.14-5.94)	-0.29 (-1.03-0.00)	<0.001
TAC (µmolTroloxEquiv/L)	3.70 (3.15-4.91)	3.25 (2.04-4.07)	0.51 (0.34-1.18)	<0.001

* median (interquartile)

Table 4: Comparison of the changing in concentrations of each variable of the Vitamin C supplement with the placebo supplement group after the study session for both T2DM groups

Variables	VitC-supplementation (n=50)	Placebo-supplementation (n=50)	*p*-value
WC (cm)	0.0 (-3.00-1.25)*	-1.0 (-3.0-2.5)*	0.838
BMI (kg/m^2)	-0.18 (-0.84-0.37)	-0.45 (-0.91-0.00)	0.285
Systolic BP (mmHg)	0.0 (-12.3-8.5)	-5.0 (-10.0-3.0)	0.317
Diastolic BP (mmHg)	1.0 (-6.3-7.3)	-1.0 (-11.5-5.0)	0.054
Glu (mg/dl)	21.0 (9.8-39.3)	-9.0 (-29.0-9.5)	<0.001
TC (mg/dl)	-2.5 (-19.3-19.0)	-11.0 (-26.5-10.0)	0.070
TG (mg/dl)	28.0 (2.0-54.0)	1.0 (-44.5-22.0)	<0.001
HDL-C (mg/dl)	-7.0 (-13.0-(-2.8))	1.0 (-11.0-8.0)	0.002
LDLc (mg/dl)	1.5 (-11.5-15.3)	1.8 (-17.0-15.5)	0.585
HbA1c (mmol/mol)	5.92 (2.77-9.06)	-4.37 (-8.75-1.64)	<0.001
TG/HDLc ratio	0.76 (0.26-2.17)	0.14 (-0.62-1.21)	0.004
Insulin (pmol/l)	1.60 (-0.30-3.13)	-0.20 (-2.05-1.45)	<0.001
HOMA-IR	0.84 (0.03-2.09)	-0.20 (-0.99-0.43)	<0.001
QUICK	-0.009 (-0.014-(-0.004)	0.004 (-0.004-0.011)	<0.001
MDA (µmol/l)	0.44 (0.11-1.31)	-0.29 (-1.03-0.00)	<0.001
TAC (µmolTroloxEquiv/L)	-0.30 (-0.54-(-0.07))	0.51 (0.34-1.18)	<0.001

* median (interquartile)

Fasting venous blood samples were collected from all participants. Blood specimens were processed and assayed at the clinical laboratory of Ladyao Hospital, Nakornsawan and Department of Medical Technology, Faculty of Medical Technology, Naresuan University. Plasma glucose (Glu), total cholesterol (TC), triglycerides (TG) and high density lipoprotein-cholesterol (HDL-C) were measured by enzymatic method on the Konelab™ Prime 60 Clinical Chemistry Analyzer (Thermo Scientific Inc, USA). LDL-C concentrations were calculated with Friedewald's formula in specimens with TG levels <400 mg/dl.

Hemoglobin A1C assay

Determination of hemoglobin A1C (HbA1c) was based on the turbidimetric inhibition immunoassay (TINIA) on hemolyzed whole blood (standardized according to the International Federation of Clinical Chemistry) by use of a Hitachi 912 auto-analyzer (Roche Diagnostic, Switzerland).

Insulin assay

Insulin levels were measured by using Axsym auto-analyzer based on microparticle enzyme immunoassay (MEIA), Abbott reagents (Abbott laboratories, Illinois, USA). All participants underwent evaluation of all insulin markers by using the Homeostasis model assessment (HOMA)-formula [14]. HOMA of insulin resistance (HOMA-IR) was defined using the following formula:

fasting glucose (mmol/l) x fasting insulin (μU/ml)/22.5, Quantitative Insulin Sensitivity Check Index (QUICKI) = 1/[LOG insulin (μU/ml) + LOG glucose (mg/dl)] [15].

Malondialdehyde (MDA) assay

The assay is based on the reaction of thiobarbituric acid with MDA to form the red (pink) chromophore of the breakdown products of peroxidized lipids called thiobarbituric acid reactive substance (TBARS). One molecule of MDA reacts with 2 molecules of TBA to yield a pink pigment with maximum absorption at 532 nm. This was measured by spectrophotometry using 1,1,3,3-tetraethoxypropane (TEP) as standard as described previously [6]. The final results were expressed as μmol of MDA formed per liters of serum. Intra-assay and inter-assay imprecision were 3.24% and 5.78%, respectively.

Total antioxidant capacity (TAC) assay

The assay is based on formation of the $ABTS^{\bullet+}$ cation [2,2'-azinobis (3-ethylbenzothiazoline-6-sulfonic acid)] and its scavenging by antioxidant sample constituents (serum) measured by spectrophotometry at 600 nm (decay of green/blue color absorption is inversely associated with antioxidant sample content and the control antioxidant is Trolox, a hydrophilic vitamin E analog) [16].

Statistical analysis

All data are presented as median and interquartile range for non-normally distributed data. The differences of these clinical data within the same subjects were analyzed by Wilcoxon signed ranks tests (2-tailed non-parametric tests) were used to assess the differences between the baseline and 60 days period after receiving supplements in both groups (intragroup) and the Mann Whitney U-test was applied for detection of the differences of intergroup (both groups) differences. *P*-values less than 0.05 were considered statistically significant. All analysis was performed using the SPSS program version 13.0 (SPSS, Chicago, IL).

RESULTS

The comparison of baseline characteristics of both VitC and placebo supplementation groups demonstrated that placebo supplementation group was slightly better glycemic control than VitC supplementation group as shown in Table 1. Fifty T2DM patients of both VitC and placebo supplementation groups were carried out the 60-days period of continuous supplement without any adverse effects and no comorbid or infection occurred to these T2DM patients. We compared all clinical characteristics at the baseline and the end of the study period of both VitC and placebo supplementation groups by using Wilcoxon signed ranks tests as shown in Table 2, 3. The present study demonstrated no weight loss and blood pressure reduction effect on VitC supplementation. In VitC supplementation group demonstrated that MDA, fasting insulin levels, HOMA-IR, fasting plasma glucose, TG, TG/HDL-C ratio and HbA1c were significantly decreased ($p<0.05$) while HDL-C, TAC and QUICKI were significantly increased ($p<0.05$). In the placebo group, we found that BMI, systolic, diastolic BP, TC, MDA, and HbA1c were significantly increased ($p<0.05$) and TAC and QUICKI were significantly decreased ($p<0.05$) at the end of the study period while glucose, TG, insulin and HOMA-IR were not significantly different but trend to increase in these markers.

We also compared the concentration change of each variable in both VitC supplementation and placebo groups. We found that insulin, HOMA-IR, MDA, glucose, HbA1c, TG, and TG/HDL-C ratio were significantly lower while QUICKI, TAC and HDL-C were significantly higher in VitC supplementation group than placebo group as shown in Table 4.

DISCUSSION

This present study demonstrated the health benefit by MDA, insulin levels, insulin resistance (HOMA-IR) glucose, TG and TG/HDL-C ratio reduction and elevation of insulin sensitivity (QUICKI), TAC and HDL-C levels in the VitC supplementation group. Increased oxidative stress is the common persistent pathogenic factor mediating the appearance of insulin resistance and proposed as increased cardiovascular risk by favoring atherosclerotic complications[17]. Many research evidences demonstrated that over-nutrition, insulin resistance, diabetes, and CVD share the major presence of an increased oxidative stress[18]. Previous studies have suggested that T2DM is a disease in which ROS are involved in the pathogenesis and the complications of T2DM[6]. Antioxidants have been demonstrated to improve insulin sensitivity both in *in vitro* and animal experiments[19,20]. Reduction of oxidative stress and increased TAC activity demonstrate beneficial effect on insulin levels, insulin resistance, insulin activity, antioxidant property[20,21] as in the present study.

Vitamin C (ascorbic acid) is a six-carbon lactone, as an antioxidant. Vitamin C is reactive but is not radical. It can form compounds with ROS or RNS (unpaired electrons or radicals). It can reduce the alpha tocopherol radical back to alpha tocopherol[22]. Vitamin C can form compound with ROS so that lipid peroxidation is inhibited. Several clinical trials have demonstrated that treatment with vitamin E, vitamin C, glutathione or cinnamon improves insulin sensitivity in insulin-resistant individuals[20,23,24], although there is evidence from molecular biology studies to support the possibility that oxidative stress alters the intracellular signaling pathway inducing insulin resistance[25]. The recent finding that insulin resistance is associated in humans with reduced intracellular antioxidant defense also supported this hypothesis[26]. Many studies demonstrated that VitC supplementation reduces blood cholesterol, triglycerides, lipid per-oxidation and increases HDL-C[27,28] and reduces the risk of cardiovascular disease[29,30]. Evidences demonstrated that increased oxidative stress enhances insulin resistance[31,32]. In insulin resistance state or decrease insulin function leads to cause dyslipidemia, as lipid triad[13,33]. So that VitC reduces either initiating oxidants or oxidized intermediates, LDL oxidation or lipid peroxidation should be decreased. This potential oxidative mechanism is consistent with our observation in the present study that MDA, a biomarker of oxidative stress, was significantly reduced and significantly increased TAC by vitamin C supplementation. According to these

mechanisms ameliorate oxidative stress and insulin resistance will improve plasma glucose, TG and HDL-C levels[13] and also in TG/HDL-C ratio. Limitation of our study, we did not analyze VitC levels in the blood circulation of the individual patients.

CONCLUSION

Vitamin C could be considered as an additional dietary supplement option to prevent and regulate underling diabetic complications along with conventional medications to treat T2DM.

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Declaration of interest: none

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