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Special Article – Vitamin C

Effect of Vitamin C Supplementation along with Endurance Physical Activity on Blood Pressure and Lipid Profile in Metabolic Syndrome Patients: A Randomized Controlled Trial

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Abstract

Background: Doing regular physical activities and consumption of antioxidants including Vitamin C are among the solutions for treatment of metabolic syndrome. This study was conducted to assess the effect of Vitamin C along with endurance physical activity on blood pressure and lipid profiles in metabolic syndrome patients.

Methods: Randomized clinical trial was carried out on 74 metabolic syndrome patients in Halabja hospital. They were divided in three groups: the first group was only on Vitamin C (500 mg/day) oral supplement (n=26). The second group was on Vitamin C (500 mg/day orally plus 30 minutes' endurance physical activity (n=23). Third group was control group (n=25) received placebo for three months. Statistical evaluation was performed by SPSS software (version 17).

Results: After supplementation with Vitamin C, the serum Vitamin C and LDL cholesterol levels increased significantly (0.001 and 0.05) with a significant reduction in the levels of triglyceride (0.001). Whereas, after supplementation of "Vitamin C plus 30 minutes' physical activity", the serum Vitamin C and HDL cholesterol levels increased significantly. No significant changes were observed in the placebo group. In addition, no significant differences were found between the study groups in terms of total cholesterol, systolic and diastolic blood pressure.

Conclusion: Daily supplementation of Vitamin C (500 mg/day) had no effect on blood pressure in metabolic syndrome patients. In addition, Vitamin C alone may play a significant role in decreasing of triglyceride, and increasing in HDL cholesterol in Vitamin C along with physical activity.

Keywords: Blood pressure; Lipid profile; Metabolic syndrome; Vitamin C

Abbreviations

MetS: Metabolic Syndrome; CVD: Cardiovascular Disease; IDF: International Diabetic Federation; HDL: High-Density Lipoprotein cholesterol; LDL: Low-Density Lipoprotein cholesterol; SD: Standard Deviation; HPLC: High Performance Liquid Chromatography; TC: Total Cholesterol; TG: Triglycerides

Introduction

The metabolic syndrome (MetS), is a collection of metabolic abnormalities. This abnormality is defined as a cluster of some risk factor of Cardiovascular Disease (CVD) like hypertensions, dyslipidemia, obesity and deficiency in glucose metabolism [1]. The estimated current global prevalence of the MetS is approximately 16% [2]. Recently, according to International Diabetic Federation (IDF) definition it is estimated that 25% of the world population have MetS [3]. Hypertension is viewed as one of the key highlights of metabolic disorder [4]. In addition, the reduction of cognitive performance has a relationship with indices of MetS like high blood pressure, low level of High Density Lipoprotein cholesterol (HDL) and obesity [5].

Observational investigation have shown inverse relationship between Vitamin C supplementation and blood pressure [6], total cholesterol and low-density lipoprotein (LDL) cholesterol [7], and positive relationship with HDL cholesterol have been reported [8]. In addition, evidence demonstrated that Vitamin C acts as an important protective role against high blood pressure, cardiac health and endothelial dysfunction through effects on nitric oxide production. As well as powerful aqueous-phase antioxidant that reduces oxidative stress [9] and prevent HDL cholesterol from oxidation [10]. Doing regular athletic activities and consuming the antioxidants are among the advised solutions for MetS patients, which are not only affecting the total safety of body, but also affect brain performance [11]. Endurance exercises produce reactive nitrogen and oxygen through the mitochondria [12]. Moreover, some of previous studies have reported that physical exercises on a regular basis promote the health of the individuals and its play a vital role in treating MetS patients [13,14].

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While most of the previous studies have focused on the effect of Vitamin C on blood pressure and plasma lipid levels, to our knowledge, no published reports are available about the effect of Vitamin C along with endurance physical activity on lipid profile and blood pressure in MetS patients. We designed randomized double blind clinical trial to assess the effect of Vitamin C along with endurance physical activity on blood pressure and lipid profiles in MetS patients.

Methods and Materials

Participants

This randomized controlled clinical trial was performed between March 2016 and May 2016 in the Halabja hospital, Kurdistan region of Iraq. In the present study, the sample size was calculated using a previously described formula for parallel clinical trials n= 2 [(z1-α/2 + z1-β) 2. s2] / d2 [15]. In this formula, n is number of participants in each group. For estimating sample size, we considered type one (α) and type two errors (β) of 0.05 and 0.20 (Power=80%) respectively, and fasting plasma glucose levels as a key variable. Based on a previous study [15], Standard Deviation (SD) of plasma glucose levels was 8 mg/dL and the difference in mean (d) was considered to be 5 mg/dL. Where α= 0.95, β=20%, study power= 80%, d= 5, and SD= 8.

$$n = \frac{2(1.96+0.85)^2 (8)^2}{(7)^2} = 21$$

We reached the sample size of 21 subjects for each group. In addition, to consider probable dropouts, 30 patients were included in each group. At the end, a total of 90 patients with MetS were included in the present study. Participants were distributed into three groups.

On the other hand, MetS was defined according to IDF criteria. According to IDF, presence of three or more of the following criteria was considered as MetS: a) waist circumference ≥94 cm for men and ≥80 cm for women, b) hypertriglyceridemia (serum triglyceride levels (TG) ≥150 mg/dl), high density lipoprotein cholesterol (HDL-C) <40 mg/dl in men and <50 mg/dl in women, c) elevated blood pressure (systolic blood pressure ≥130 or diastolic blood pressure ≥85 mmHg), and d) elevated fasting plasma glucose ≥100 mg/dl [16]. A total of 90 patients with MetS (aged 30-60 years) were included in this study. Individuals who were using any kind of minerals, Vitamins and medications, diabetic patients, smokers, alcohol users, pregnant or lactating women, post-menopausal women, patients with a history of bariatric surgery and those that were on a weight loss diet were excluded from this study. We also did not include those with a high TG levels (more than 400 mg/dl) and those with high systolic or diastolic blood pressure (>140/90 mmHg).

The ethical committee of Tehran University of Medical Sciences approved the study protocol (Ethical code: IR.TUMS.REC.1395.2832). This study was registered online at the Iranian website for registry of clinical trials (IRCT20161110030823N2). All participants provided informed written consent before participating in the study.

Procedures

Participants gave their written informed consent and then underwent the following baseline investigations. **First**, Blood pressure was measured at morning time in the seated position using a standard mercury sphygmomanometer after at least 15 minutes of rest. **Second**, fasting blood samples were collected at baseline and 12 weeks of intervention after 12 hours overnight fasting for estimation of plasma ascorbic acid and blood lipids. High performance liquid chromatography (HPLC method) used to measure the total serum Vitamin C. The reference range of Vitamin C is 0.6-2 mg/dL. Less than 0.6 will be defined as deficient [17]. Serum Total Cholesterol (TC) and Triglycerides (TG) concentration were assayed using enzymatic colorimetric tests with cholesterol esterase and cholesterol oxidase and glycerol phosphate oxidase, respectively, by using standard kits following manufacturer's protocols [18]. HDL cholesterol was measured after precipitation of the Apo lipoprotein B containing lipoproteins with phosphor-tungstic acid. Plasma LDL cholesterol was estimated using the Fried Wald formula (LDL cholesterol = TC - [HDL - (TG/2.2)]) [19]. **Third**, participants were then randomly assigned to three groups: Group 1 received Vitamin C supplements (500 mg/day) without endurance physical activity (n=30); group 2 received Vitamin C supplements (500 mg/day) with 30 minutes' endurance physical activity (n=30); and group 3 received one placebo of Vitamin C/day without endurance physical activity (n=30) (Figure 1). Regarding physical activity assessment; two times a week for climbing (around 2 hours each time) and two times a week for running (around one hour in the afternoon between 3 to 5 PM). Approximately six hours per week all together [20]. The Vitamin C supplements and placebos manufactured by Osweh Company (Tehran, Iran). Placebos were on the same shape, odor and size of the Vitamin C supplements. Participants were asked to use Vitamin C supplements and placebos for 12 weeks. Compliance of study participants with the Vitamin C supplements was assessed through quantification of serum Vitamin C.

Statistical analysis

We used Kolmogorov-Smirnov test to examine the normal distribution of variables. The analyses were done based on intention-to-treat approach. Missing values were treated based on Last-Observation-Carried-Forward method. Baseline general characteristics among different groups were examined using one-way ANOVA for continuous variable and a chi-square test for categorical variables. To determine the effects of Vitamin C supplementation and endurance physical activity on lipid profiles and blood pressure, we used one-way ANOVA. We used Tukey's post-hoc comparisons to identify pairwise differences when we reached a significant finding in ANOVA. P<0.05 was considered as statistically significant. All statistical analyses were done using the Statistical Package for Social Science version 17 (SPSS Inc., Chicago, Illinois, USA).

Results

Baseline demographic characteristics of the study participants

In the present study, 90 MetS patients were enrolled: Vitamin C (n=30), "Vitamin C plus physical activity" (n=30), and placebo (n=30) groups. The study procedure is shown in Figure 1. In the present study, 16 participants excluded from the study because of the following reasons: 4 from Vitamin C group [(pregnancy (n=1), (did not follow recommended Vitamin C intake n= 3)], 7 from Vitamin plus physical activity group [(did not follow recommended physical activity (n=5), (did not follow recommended Vitamin C intake (n=2)], and 5 from placebo group [(did not complete trial (n=5)]. Finally, 74 subjects remained in the study (59.5% females, 40.5%

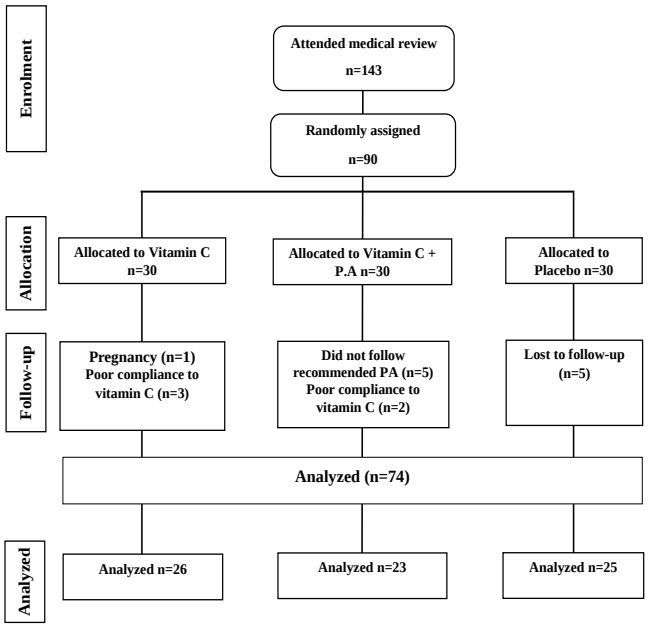

Figure 1: Flow chart for inclusion and exclusion in the study.

males). The baseline demographic characteristics of study participants are presented in Table 1. The mean age of the patients with MetS in Vitamin C group (41.2 ± 5.8 years), Vitamin C plus physical activity group (40.8±5.8 years), and placebo group (42.6±5.6 years) was not significantly different from each other. In addition, the distribution of participants in terms of family history of obesity, diabetes mellitus and blood pressure was not significantly different among groups.

Baseline and end of trial characteristics of the study participants

Both baseline and end of trial characteristics of study participants are presented in Table 2. There were no significant differences among the three groups in terms of systolic and diastolic blood pressure. The baseline metabolic profile of study participants revealed no significant differences in TC levels among the three intervention groups. However, participants who received Vitamin C supplements had higher serum levels of TG compared with those who received "Vitamin C plus physical activity" or placebo (268.4±107.2 vs. 176.1±87.4 and 147.4±43 mg/dl, P<0.001). Participants in the Vitamin C plus physical activity group had higher levels of HDL cholesterol compared with other groups. In addition, participants in the Vitamin C group had lower levels of LDL cholesterol compared with those in the placebo group but not reach a significant level. Furthermore, we observed a significant increase in mean serum Vitamin C concentrations in participants who received Vitamin C (0.9±0.4 mg/dl at study baseline vs. 1.4±0.3 mg/dl at the end of the study, P<0.001) or "Vitamin C plus physical activity" (0.8±0.3 mg/dl at study baseline vs. 1.7±0.3 mg/dl at the end of the study, P<0.001). No significant changes in serum levels of Vitamin C were seen in participants in the placebo (0.9±0.3 mg/dl at study baseline vs. 1.1±0.3 mg/dl at the end of the study, P=0.1) groups after the intervention. End of trial mean "Vitamin C plus physical activity" group could significantly increase HDL cholesterol compared with the Vitamin C and placebo groups (51.9±20.6 vs. 33.2±10.1 and 31.8±7.1, P<0.001), and significant decrease in TG was observed in Vitamin C group (p=0.001). Moreover, there were no significant effects on means of TC, systolic and diastolic blood pressure at the end of the study among three groups.

Table 1: Baseline demographic characteristics of study participants[1].

Groups (n=74)				
Variables	Vitamin C[2] (n=26)	Vitamin C+PA[3] (n=23)	Placebo[4] (n=25)	P-value[5]
Age, y	41.2±5.8	40.8±5.8	42.6±5.6	0.51
Female, %	62	70	48	0.5
Family history of obesity, %	65	65	76	0.7
Family history of DM, %	46	35	60	0.2
Family history of blood pressure, %	46	57	60	0.6

[1]Data are mean ± standard deviation (SD)
[2]Receiving 500 mg Vitamin C per day
[3]Receiving 500 mg Vitamin C per day plus 30 minutes' endurance physical activity
[4]Receiving one placebo per day
[5]Obtained from ANOVA or chi-square test, where appropriate
PA: Physical Activity; DM: Diabetes Mellitus

Changes in biochemical indicators across the study groups

Changes in biochemical indicators across three study groups are presented in Table 3. A significant changes in serum levels of TG were seen following Vitamin C and "Vitamin C plus physical activity" than that in the placebo group (P<0.01). In addition, a significant changes of HDL cholesterol were seen following "Vitamin C and physical activity" group than in Vitamin C and placebo group (P=0.001). No significant changes in levels of systolic and diastolic blood pressure, TC and LDL cholesterol were seen among the three groups. Finally, no serious adverse event was reported, and no abnormalities in laboratory test were found during trial period.

Discussion

After the studies, which showed role of Vitamin C supplementation to lower the level of cholesterol in patients of hypercholesterolemia [21], a chain of similar studies was continued. It has been found that ascorbic acid increases HDL cholesterol and decreases TG, lipid peroxidation and blood cholesterol [22]. Study also proved that presence of Vitamin C reduce the blood lipid profile in hypercholeterolemic patients [23]. Another study showed increase in HDL cholesterol and decrease in LDL cholesterol levels upon administration of Vitamin C in subjects [24].

Two different finding are presented in the study groups, the first primary finding of present study is a significant decrease in TG and an increase in LDL cholesterol and plasma ascorbic acid level after Vitamin C supplementation. The second finding, after supplementation of "Vitamin C plus 30 minutes of physical activity" the serum Vitamin C and HDL cholesterol increased significantly. No change was found between the study groups in term of TC, systolic and diastolic blood pressure among all three groups.

The result of present study is in line with previous trial showing that, no change appeared in TC but TG was found to be significantly reduced after 8 weeks of 500 mg of Vitamin C supplementation [25]. In contrast Vitamin C could significantly reduce plasma levels of TC [13]. Other observational investigation shows that no change

Table 2: Baseline and end of trial means of blood pressure and lipid profiles across study groups[1].

Groups (n=74)							
Variables	**Vitamin C[2]**	**P-value[5]**	**Vitamin C+PA[3]**	**P-value[5]**	**Placebo[4]**	**P-value[5]**	**P-value[6]**
SBP (mmHg) Baseline	130.2±12	0.5	128.9±11.4	0.4	125.6±14.5	0.5	0.4
SBP (mmHg) After 12 weeks	129.2±8.6		173±252.4		126.6±12		0.4
DBP (mmHg) Baseline	81.3±8.3	0.7	79.3±7.1	0.9	80±6.9	0.4	0.6
DBP (mmHg) After 12 weeks	81.9±4.9		79.6±4.5		81.6±6.7		0.3
TC (mg/dl) Baseline	174.8±41.5	0.3	178.3±29.8	0.5	185.9±39	0.1	0.6
TC (mg/dl) After 12 weeks	180.2±31.9		175.1±29.9		196.8±39.4		0.07
TG (mg/dl) Baseline	268.4±107.2*	0.001	176.1±87.4#	0.09	147.4±43	0.07	<0.001
TG (mg/dl) After 12 weeks	246.1±90.3*		151.2±53.8#		158.6±35.4		0.001
LDL-C (mg/dl) Baseline	114.5±47.5$	0.05	135.5±32.7	0.9	150.4±39.8	0.2	0.009
LDL-C (mg/dl) After 12 weeks	124.3±39.6$		134.5±28.2		158.8±39.1		0.004
HDL-C (mg/dl) Baseline	33±13.5	0.9	37.7±11	0.002	30±8.5	0.2	0.07
HDL-C (mg/dl) After 12 weeks	33.2±10.1		51.9±20.6*		31.8±7.1		0.001
Vitamin C Baseline	0.9±0.4	<0.001	0.8±0.3	<0.001	0.9±0.3	0.5	0.2
Vitamin C After 12 weeks	1.4±0.3		1.7±0.3		0.9±0.3		0.001

[1]Data are means ± standard deviation (SD)
[2]Receiving 500 mg Vitamin C per day
[3]Receiving 500 mg Vitamin C per day plus 30 minutes' endurance physical activity
[4]Receiving one placebo per day
[5]Obtained from pared t-test
[6]Obtained from ANOVA
*P<0.05 compared to other groups
#P<0.05 compared to Vitamin C
$P<0.05 compared to placebo
PA: Physical Activity; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; TC: Total Cholesterol; TG: Triglycerides; LDL-C: Low-Density Lipoprotein Cholesterol; HDL-C: High-Density Lipoprotein Cholesterol

in lipid profile in diabetic patients after 1000 mg/day Vitamin C supplementation for one month except in HDL cholesterol [26]. Finding from observational study shows that Vitamin C supplemented in dose of 1000 mg/day within a period of 8 weeks can lower a serum TC level in young people. In addition, when same dose and longer duration taken six to 12 month by older population the change in TC was less compared to young population (29±9 years) in first six month, but no significant change in 2000 mg/day of Vitamin C supplementation in older age group (58±3 years) for the second six months [7].

In most cases, there are LDL cholesterol differences in study groups. However, this issue depends on the given circumstances. The density of lipoprotein varies from one case to the other and from healthy to unhealthy people. Finding from current study, shows significant changes in LDL cholesterol during the study among three groups (P<0.004). Viewed differently, it is important to point out that LDL cholesterol is directly proportional to the physical exercises that an individual participates, and Vitamin C that they consume.

Previous research further indicates that comparisons using Bonferroni method reveal that consuming Vitamin C or taking Vitamin C and exercises happen to increase Vitamin C level compared with placebo [27]. The veracity of this information is exactly what was seen in the present research. The values obtained read as (1.4±0.3 and 1.7±0.3; p<0.001 vs 0.9±0.3; p=0.5 respectively). As a matter of general cognition, the consumption of Vitamin C and exercises a is bound to increase Vitamin C level more as compare to with Vitamin C alone. The above positions suggest that once a person undertakes exercises, the rate of metabolism increases, and this assists in the breaking down of essential body nutrients. In reference to the fact that Vitamins are necessary for the development of body tissues and cells, it is recommended that proper and enough exercises have to be encouraged for Vitamins C to be dissolved well [28]. As seen in the above highlights, it is evident that the present research relates with the facts that have been gathered over time as far as the digestion and breaking down of Vitamins and the participation of physical exercises are concerned [29].

Studies have showed that in case of oxidative stress Vitamin C protects the body from its adverse effects by inhibiting oxidation of lipids in human plasma [30]. *In vitro* studies showed that Vitamin C prevents LDL cholesterol oxidation and serve as antioxidant [31]. The oxidized LDL cholesterol or smoking can induce the interaction of endothelial cells with leukocytes, which in turn results in the development of atherosclerosis. Studies have shown that in vivo Vitamin C inhibits this interaction [32,33].

Vitamin C is also found to decrease peroxidation of LDL cholesterol [34]. It has been shown to prevent white blood cells adhesion to arteries that are damaged and participate in the collagen synthesis hence strengthen the walls of arteries and prevents atherosclerosis [30].

In contrast to present study, the use of Vitamin C supplements known to improve systolic and diastolic blood pressure in patients with hypertension [35]. Melissa and Ock alos summarized the

Table 3: Changes in blood pressure and lipid profile across study groups[1].

	Groups			
Variables	**Vitamin C[2]**	**Vitamin C+PA[3]**	**Placebo[4]**	**P-value[5]**
SBP (mmHg)	-0.96±8	44.1±251.1	1±8.2	0.5
DBP (mmHg)	0.57±7.39	0.21±8.2	1.6±8.7	0.8
TC (mg/dl)	5.38±24.8	-3.1±22.3	10.9±32.7	0.2
TG (mg/dl)	22.3±31.2*	-24.9±68.8*	11.2±29.7	0.01
LDL-C (mg/dl)	9.8±24.7	-1±27.7	8.3±30.9	0.4
HDL-C (mg/dl)	0.1±11.1†	14.3±20‡	1.7±7.2	0.001
Vitamin C	0.5±0.5	0.9±0.4	-0.07±0.5	<0.001

[1]Data are means ± standard deviation (SD)
[2]Receiving 500 mg Vitamin C per day
[3]Receiving 500 mg Vitamin C per day plus 30 minutes' endurance physical activity
[4]Receiving one placebo per day
[5]Obtained from ANOVA
*P<0.05 compared with placebo group
†P<0.05 compared with Vitamin C plus physical activity
‡P<0.05 compared with Vitamin C and placebo
PA: Physical Activity; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; TC: Total Cholesterol; TG: Triglycerides; LDL-C: Low-Density Lipoprotein Cholesterol; HDL-C: High-Density Lipoprotein Cholesterol

meta-analysis studies investigating the effects of Vitamin C on cardiovascular disease markers like arterial stiffness; lipid profile, endothelial function, and blood pressure, showed that Vitamin C reduce blood pressure and improve endothelial function. Vitamin C along with Vitamin E reduce arterial stiffness [36]. Vitamin C has long been known to participate in several important functions in the vascular bed in support of endothelial cells. These functions include increasing the synthesis and deposition of type IV collagen in the basement membrane, stimulating endothelial proliferation, inhibiting apoptosis, scavenging radical species, and sparing endothelial cell-derived nitric oxide to help modulate blood flow. Although ascorbate may not be able to reverse inflammatory vascular diseases such as atherosclerosis, it may well play a role in preventing the endothelial dysfunction that is the earliest sign of many such diseases [37].

On the other hand, results from most clinical intervention trials have failed to show a beneficial effect of Vitamin C supplementation on the primary or secondary prevention of CVD. In the Women's Antioxidant Cardiovascular Study, a secondary prevention trial involving 8,171 women aged 40 years or older with a history of cardiovascular disease, supplementation with 500 mg/day Vitamin C for a mean of 9.4 years showed no overall effect on cardiovascular events [38]. Similarly, Vitamin C supplementation (500 mg/day) for a mean follow-up of 8 years had no effect on major cardiovascular events in male physicians enrolled in the Physicians' Health Study II [39]. The results of our study support these findings.

The main limitations of this study is its small sample size and duration is short which limits the generalizability of our results. However, studies with a larger sample size and longer follow-up period together with measurement of other related Vitamins levels may yield more meaningful data on the effects of Vitamins supplementations on MetS patients. The main strength of this study was being the first study, which describes the combined impact of Vitamin C and endurance physical activity on blood pressure and lipid profiles in patients with MetS.

Finally, we conclude that daily supplementation of Vitamin C (500 mg/day), had no effect on blood pressure in MetS patients. In addition, Vitamin C alone may play a significant role in decreasing of TG, and increasing in HDL cholesterol in Vitamin C along with physical activity.

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