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Vitamin C supplementation lowers serum low-density lipoprotein cholesterol and triglycerides: a meta-analysis of 13 randomized controlled trials

Marc P. McRae MSc, DC, FACN, DACBN*

Assistant Professor, Department of Physiology and Biochemistry, National University of Health Sciences, Lombard, IL 60148

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Abstract

Objective: Vitamin C has been shown to be an effective therapeutic for reducing total serum cholesterol, but epidemiologic studies have determined that low-density lipoprotein (LDL) cholesterol and high-density lipoprotein (HDL) cholesterol are actually better predictive measures of coronary heart disease risk. Therefore, the purpose of this study was to provide a comprehensive meta-analysis of randomized controlled trials to investigate the effect of vitamin C supplementation on LDL and HDL cholesterol as well as triglycerides in patients with hypercholesterolemia.

Methods: Thirteen randomized controlled trials published between 1970 and June 2007 were identified using Medline and a manual search. From the 13 trials, 14 separate group populations with hypercholesterolemia and who were supplemented with at least 500 mg/d of vitamin C for between 3 and 24 weeks were entered into the meta-analysis. This meta-analysis used a random-effects model; and the overall effect sizes were calculated for changes in LDL and HDL cholesterol, as well as triglyceride concentrations.

Results: The pooled estimate of effect for vitamin C supplementation on LDL and HDL cholesterol was −7.9 mg/dL (95% confidence interval [CI], −12.3 to −3.5; $P = .000$) and 1.1 mg/dL (95% CI, −0.2 to 2.3; not significant), respectively. The pooled estimate of effect for vitamin C supplementation on triglycerides was −20.1 mg/dL (95% CI, −33.3 to −6.8; $P < .003$).

Conclusion: Supplementation with at least 500 mg/d of vitamin C, for a minimum of 4 weeks, can result in a significant decrease in serum LDL cholesterol and triglyceride concentrations. However, there was a nonsignificant elevation of serum HDL cholesterol.

Introduction

Hypercholesterolemia is a primary risk factor leading to coronary heart disease, which is the leading cause of premature death and disability in the United

* Department of Physiology and Biochemistry, National University of Health Sciences, 200 East Roosevelt Rd, Lombard, IL 60148, USA. Tel.: +1 630 889 6592.
E-mail address: mmcrae@nuhs.edu.

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States. The American Heart Association estimates that approximately 36.6 million American adults have total serum cholesterol levels of greater than 240 mg/dL.[1] Over the past couple of decades, a number of nutritional compounds have shown some promise in reducing total serum cholesterol concentrations. One such compound is vitamin C, and a recent meta-analysis found that supplementation with at least 500 mg/d can reduce total serum cholesterol in both borderline-high and high hypercholesterolemic groups by 7.6 and 17.2 mg/dL, respectively.[2] A pooled analysis of 9 cohort studies found that those who took at least 700 mg of vitamin C had a 25% reduction in the incidence of coronary heart disease.[3] Although total serum cholesterol concentration is a well-known predictor of the incidence of coronary heart disease, a number of epidemiologic studies have determined that low-density lipoprotein (LDL) cholesterol and high-density lipoprotein (HDL) cholesterol are actually better predictive measures of coronary heart disease risk.[4-9] The Helsinki Heart Study determined that the LDL/HDL ratio was the best single predictor of cardiac events.[10] The role of triglycerides in predicting coronary heart disease remained controversial up until the 8-year follow-up study to the Copenhagen study that found that triglycerides were actually a strong independent risk factor for predicting coronary heart disease.[11] This finding was further supported by a meta-analysis of 17 population-based prospective studies that found that plasma triglycerides predict subsequent coronary heart disease.[12]

It is because of these findings that the National Cholesterol Education Program Expert Panel revised its guidelines and now recommends monitoring triglycerides, LDL cholesterol, and HDL cholesterol in the context of coronary heart disease risk factors.[13] Therefore, in light of the fact that vitamin C has been shown to be an effective therapeutic for total serum cholesterol reduction, the purpose of this study was to provide a comprehensive meta-analysis of randomized controlled trials to investigate the effect of vitamin C supplementation on LDL and HDL cholesterol as well as triglycerides in patients with hypercholesterolemia.

Methods

Selection of studies

A comprehensive Medline literature search was performed to locate relevant randomized controlled trials published between 1970 and June 2007. The following headings were combined using the following Boolean operation: (*vitamin C* OR *ascorbic acid* OR *ascorbate*) AND (*cholesterol* OR *triglyceride* OR *triglycerides*). The search was restricted to key terms located in the title/abstract, and language was not an exclusion criteria. Furthermore, only full-length original journal articles were considered; and no attempt was made to include abstracts or unpublished studies. A manual search was also conducted by using reference lists from original research papers and review articles.

To be included in the meta-analysis, a study had to meet the following criteria: (1) the study was conducted using hypercholesterolemic human subjects (total serum cholesterol >200 mg/dL); (2) the study design consisted of at least a single-blind, random allocation of study participants to vitamin C treatment or placebo-controlled groups; (3) vitamin C was given orally with a minimum dose of 500 mg/d; (4) the intervention was greater than 3 weeks and less than 24 weeks; and (5) the study reported the mean LDL cholesterol, HDL cholesterol, and triglyceride concentration changes in both the treatment and control groups. The dose and intervention duration cutoffs were chosen based on the observations that 500 mg/d is the required intake for 95% of the population to achieve a saturated plasma vitamin C concentration[14] and that it takes 3 to 4 weeks to reach a plasma steady-state after vitamin C supplementation.[15]

Only 13 studies of the potential 1363 abstracts met the eligibility criteria and were included in the meta-analysis.[16-28] Fourteen separate vitamin C supplementation groups were identified from these 13 studies. Participant and study design characteristics for the 14 groups included in the meta-analysis are presented in Table 1.

Data abstraction and statistical analysis

Information on sample size, participant characteristics, study design, vitamin C dosage, duration of intervention, and treatment results with the 3 lipid categories (LDL, HDL, and triglycerides) were abstracted from the 13 studies. In the end, 11 separate LDL cholesterol, 12 HDL cholesterol, and 10 triglyceride group populations were identified from the 13 studies. The pooled demographics for each lipid category are presented in Table 2.

To calculate the overall effect size within each lipid category measurement, studies were weighted by the reciprocal of their variances. The variances for all groups were calculated using the variances at baseline and at the end of follow-up based on the methodology

Table 1 Participant and study design characteristics of the 14 vitamin C supplementation groups

Source and Year (Reference)	Sample Size	Mean Age (y)	Male (%)	Study Design	Vitamin C Dose (mg/d)	Duration (wk)	Baseline Lipids (mg/dL)		
							LDL Cholesterol	HDL Cholesterol	Triglyceride
Horsey et al 1981[16]	11	82	55	PD	1000	6	139.4	35.9	
Wahlberg and Walldius 1982[17]	9	55	89	XD	2000	4	154.4	42.1	427.1
Bishop et al 1985[18]	25	51	52	XD	500	8			208.2
Bishop et al 1985[18]	25	60	44	XD	500	8			288.0
Aro et al 1988[19]	27	48	0	XD	2000	6		44.8	
Salonen et al 1991[20]	39	72	100	PD	600	20	146.7	49.4	
Cerna et al 1992[21]	80	48	42	PD	500	24	203.1	53.7	196.7
Paolisso et al 1995[22]	40	72	48	XD	1000	16	220.1	42.5	231.2
Gokce et al 1999[23]	21	56	81	PD	500	4	123	39	223
Fotherby et al 2000[24]	40	72	50	XD	500	12	135.1	60.2	
Singhal et al 2001[25]	31	55	77	PD	1000	4	120.7	43.8	214.4
Vinson and Jang 2001[26]	10	53	70	PD	1000	8	193.1	51.7	150.6
Rezaian et al 2002[27]	30	>50	50	PD	1000	10	120.8	33.3	152.8
Shidfar et al 2003[28]	17	52	35	PD	500	10	160.6	37.2	315

PD, Parallel double-blind; *XD*, crossover double blind.

of Follmann et al.[29] In this method, a correlation coefficient of 0.5 between the initial and final measures was assumed. Within each trial, equal variance was assumed between the control and intervention groups, as well as between the beginning and end of each trial. For parallel and crossover trials, net changes in measurements were calculated as follows: (measure at end of follow-up in the treatment group − measure at baseline in the treatment group) − (measure at end of follow-up in the control group − measure at baseline in the control group).

Estimates of the mean effect of vitamin C supplementation on each lipid measure and the corresponding 95% confidence intervals (CIs) were calculated using random-effects models. The assumption of heterogeneity implied by the use of the random-effects model was plausible because of differences between trials in such aspects as duration of the trial, dosages used, and sample populations that differed by age and sex. To examine potential publication bias, a funnel plot was constructed where the sample size of each study was plotted against its corresponding effect size. Data analysis was performed using Comprehensive Meta-Analysis software version 2.0 (Biostat, Englewood, NJ).

Table 2 Pooled demographic of subjects included in the meta-analysis for each lipid profile

	Vitamin C Group	Placebo Group
	LDL Cholesterol	
No. of Subjects	328	310
Age (y)	58.3	59.6
% Male	59.1	61.3
Baseline LDL (mg/dL)	163.7	154.6
	HDL Cholesterol	
No. of Subjects	355	338
Age (y)	60.2	61.5
% Male	54.6	56.4
Baseline HDL (mg/dL)	46.9	47.2
	Triglycerides	
No. of Subjects	289	270
Age (y)	55.3	56.2
% Male	52.9	54.8
Baseline Triglycerides (mg/dL)	222.2	231.5

Results

Characteristics of the studies

The 11 groups making up the LDL cholesterol category consisted of a total of 549 individual subjects (328 participated in the vitamin C supplementation treatment group, and 310 participated in the control group). All of the trials were conducted using adults with an age range of 48 to 82 years and a pooled mean age of 58.9 years. Men made up most of the subjects, with the pooled population consisting of 60% men. Eight trials used a parallel double-blind design, and 3

used a crossover double-blind design. The study duration varied from 4 to 24 weeks, with a median length of 10 weeks. Vitamin C supplementation for 5 of the 11 trials was 500 to 600 mg/d, whereas 5 trials used 1000 mg/d and 1 used 2000 mg/d. The pooled mean baseline LDL cholesterol concentrations for the treatment and control groups were 163.7 and 154.6 mg/dL, respectively. Comparative demographics between the placebo and vitamin C supplementation groups are presented in Table 2.

The 12 groups making up the HDL cholesterol category consisted of a total of 577 individual subjects (355 participated in the vitamin C supplementation treatment group, and 338 participated in the control group). All of the trials were conducted using adults with an age range of 48 to 82 years and a pooled mean age of

Table 3 Mean net change in LDL cholesterol, HDL cholesterol, and triglycerides after vitamin C supplementation

Source and Year (Reference)	Sample Size	Net Lipid Change [a] (95% CI)	*P* Value [b]
LDL Cholesterol			
Horsey et al 1981[16]	25	−13.9 (−32.3, 4.5)	NS
Wahlberg and Walldius 1982[17]	18	1.2 (−31.0, 33.3)	NS
Salonen et al 1991[20]	78	3.9 (−6.3, 14.0)	NS
Cerna et al 1992[21]	134	−17.8 (−29.5, −6.0)	.004
Paolisso et al 1995[22]	80	−57.9 (−91.4, −24.4)	.001
Gokce et al 1999[23]	46	−1.0 (−13.2, 11.2)	NS
Fotherby et al 2000[24]	80	−3.9 (−14.0, 6.3)	NS
Singhal et al 2001[25]	63	−1.9 (−14.0, 10.2)	NS
Vinson and Jang 2001[26]	18	−34.0 (−67.3, −0.7)	NS
Rezaian et al 2002[27]	60	−26.5 (−44.9, −8.0)	.007
Shidfar et al 2003[28]	36	−21.7 (−40.5, −2.9)	.030
HDL Cholesterol			
Horsey et al 1981[16]	25	7.3 (−0.7, 15.4)	NS
Wahlberg and Walldius 1982[17]	18	−1.5 (−7.8, 4.7)	NS
Aro et al 1988[19]	54	−1.5 (−5.0, 1.9)	NS
Salonen et al 1991[20]	78	−1.9 (−5.8, 1.9)	NS
Cerna et al 1992[21]	135	2.3 (−1.1, 5.8)	NS
Paolisso et al 1995[22]	80	3.9 (−3.7, 11.4)	NS
Gokce et al 1999[23]	46	−4.0 (−8.4, 0.4)	NS
Fotherby et al 2000[24]	80	1.2 (−3.1, 5.4)	NS
Singhal et al 2001[25]	63	0.3 (−3.4, 4.0)	NS
Vinson and Jang 2001[26]	18	−0.8 (−8.4, 6.8)	NS
Rezaian et al 2002[27]	60	11.7 (8.0, 15.3)	.000
Shidfar et al 2003[28]	36	−1.4 (−4.9, 2.1)	NS
Triglycerides			
Wahlberg and Walldius 1982[17]	18	59.4 (−62.3, 181.0)	NS
Bishop et al 1985[18]	50	−43.4 (−99.9, 13.1)	NS
Bishop et al 1985[18]	50	4.4 (−68.5, 77.4)	NS
Cerna et al 1992[21]	138	0.9 (−44.7, 46.5)	NS
Paolisso et al 1995[22]	80	−44.3 (−72.1, −16.5)	.003
Gokce et al 1999[23]	46	27.0 (−28.5, 82.5)	NS
Singhal et al 2001[25]	63	−33.5 (−68.0, 1.0)	NS
Vinson and Jang 2001[26]	18	18.6 (−32.2, 69.4)	NS
Rezaian et al 2002[27]	60	−11.1 (−37.9, 15.8)	NS
Shidfar et al 2003[28]	36	−52.7 (−103.3, −2.1)	.049

NS, Not significant.

[a] For parallel trials, the net change is (intervention final lipid − baseline lipid) − (control final lipid − baseline lipid). For crossover trials, the net change is intervention final lipid − control final lipid.

[b] The *P* value was calculated by the author.

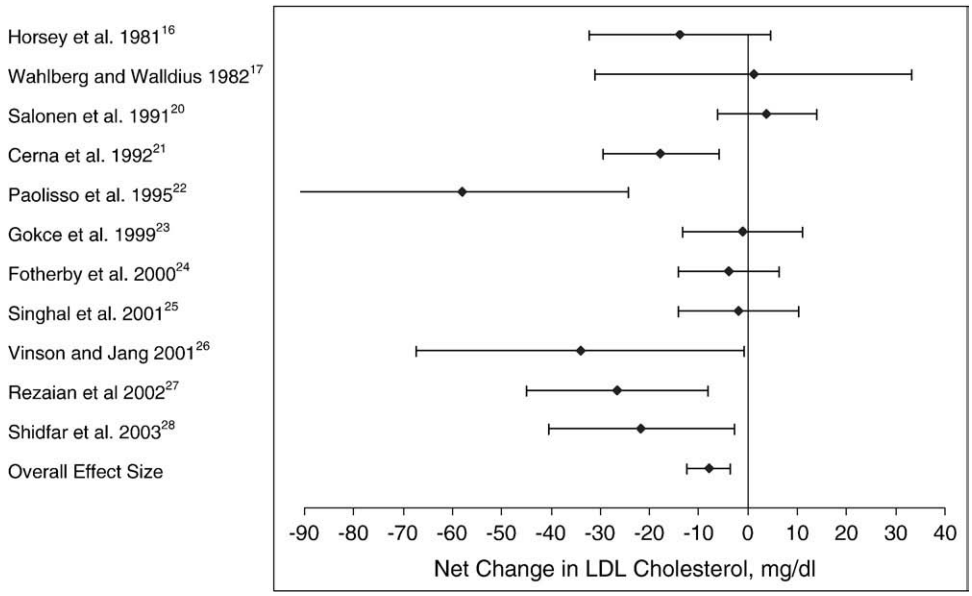

Fig 1. Net change (and 95% CI) in LDL cholesterol concentration associated with vitamin C supplementation. The overall effect size is weighted by the inverse of the total variance of each trial.

60.8 years. Men made up most of the subjects, with the pooled population consisting of 55% men. Eight trials used a parallel double-blind design, and 4 used a crossover double-blind design. The study duration varied from 4 to 24 weeks, with a median length of 10 weeks. Vitamin C supplementation for 5 of the 12 trials was 500 to 600 mg/d, whereas 5 trials used 1000 mg/d and 2 used 2000 mg/d. The pooled mean baseline HDL cholesterol concentrations for the treatment and control groups were 46.9 and 47.2 mg/dL, respectively.

The 10 groups making up the triglyceride category consisted of a total of 460 individual subjects (289 participated in the vitamin C supplementation treatment group, and 270 participated in the control group). All of the trials were conducted using adults with an age range of 48 to 72 years and a pooled mean age of 55.7 years. Men made up most of the subjects, with the pooled population consisting of 54% men. Six trials used a parallel double-blind design, and 4 used a crossover double-blind design. The study duration varied from

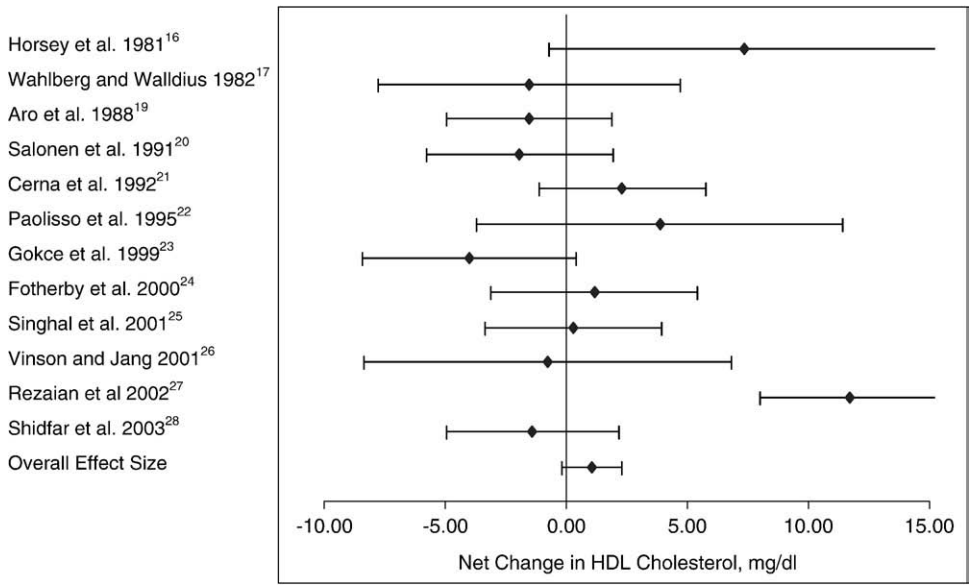

Fig 2. Net change (and 95% CI) in HDL cholesterol concentration associated with vitamin C supplementation. The overall effect size is weighted by the inverse of the total variance of each trial.

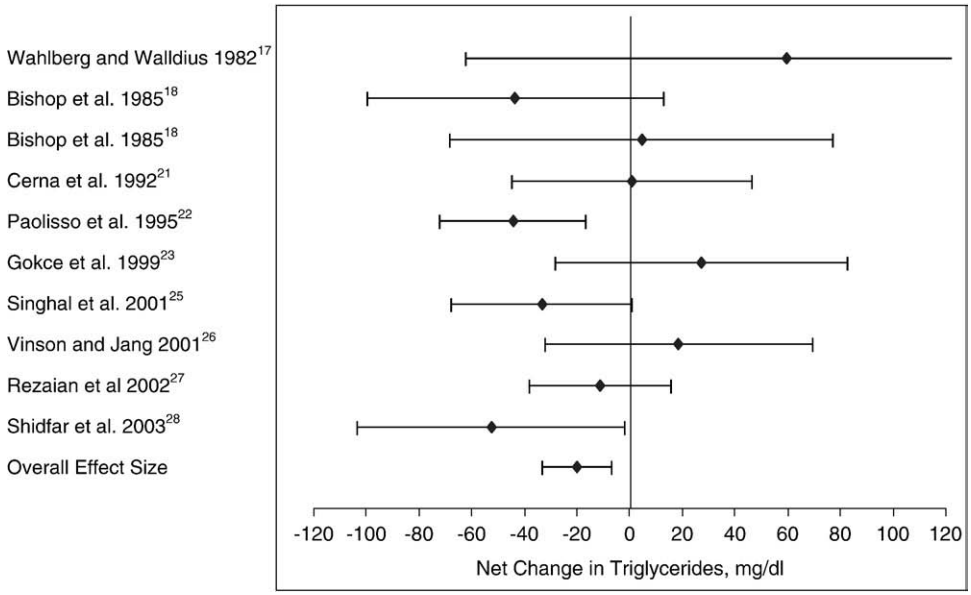

Fig 3. Net change (and 95% CI) in triglyceride concentration associated with vitamin C supplementation. The overall effect size is weighted by the inverse of the total variance of each trial.

4 to 24 weeks, with a median length of 8 weeks. Vitamin C supplementation for 5 of the 10 trials was 500 mg/d, whereas 4 trials used 1000 mg/d and 1 used 2000 mg/d. The pooled mean baseline triglyceride concentrations for the treatment and control groups were 222.2 and 231.5 mg/dL, respectively.

Serum lipid concentration changes

The mean net changes between the treatment and placebo groups for LDL cholesterol, HDL cholesterol, and triglycerides entered into the meta-analysis are presented in Table 3. In the LDL cholesterol category, 9 of the 11 trials had an intervention-related trend toward a reduction in LDL cholesterol; but only 4 of these trials showed a statistically significant reduction ($P < .05$) when compared with the control group (Fig 1). For the HDL cholesterol category, a trend toward an intervention-related increase was observed for 6 of the 12 trials; however, only 1 of these trials showed a statistically significant increase when compared with the control group (Fig 2). For the triglyceride category, a trend toward intervention-related reduction was also observed for 5 of the 10 trials; but only 2 of these trials showed a statistically significant reduction when compared with the control group (Fig 3).

The effect size along with the 95% CIs for each trial, as well as the overall effect size for the 3 lipid categories, are presented in Table 4 and Figs 1 through 3. For LDL cholesterol, the overall pooled estimate of the effect of vitamin C supplementation on LDL cholesterol was −7.9 mg/dL (95% CI, −12.3 to −3.5; $P = .000$). For HDL cholesterol, the overall pooled estimate of the effect of vitamin C supplementation on HDL cholesterol was 1.1 mg/dL (95% CI, −0.2 to 2.3; not significant). For triglycerides, the overall pooled estimate of the effect of vitamin C supplementation on triglycerides was −20.1 mg/dL (95% CI, −33.3 to −6.8; $P < .003$).

Publication bias

For all 3 lipid profiles, the plot of sample size vs effect size showed a typical "funnel" shape with little variation in effect size for large sample studies and

Table 4 Pooled estimates of treatment effect on the lipid profile

Variables	No. of Study Groups	Sample Size	Effect Size (95% CI)	Percentage Change	*P* Value
Total Cholesterol [a]	18	1119	−10.67 (−14.0, −7.3)	4.5	.000
LDL Cholesterol	11	638	−7.9 (−12.3, −3.5)	5.0	.000
HDL Cholesterol	12	692	1.1 (−0.2, 2.3)	2.3	.087
Triglycerides	10	555	−20.1 (−33.3, −6.8)	8.8	.003

[a] Data for total cholesterol extrapolated from McRae.[2]

increasing spread of effect size with smaller sample sizes (data not shown). The distribution of effects sizes seen in the individual studies was symmetrically distributed around the pooled mean effect size for the LDL cholesterol and triglyceride category, but asymmetrically distributed for the HDL cholesterol category (Figs 1-3).

Discussion

In this current meta-analysis, vitamin C supplementation provided a significant reduction in both LDL cholesterol (−7.9 mg/dL or 5%) and triglycerides (−20.1 mg/dL or 8.8%), but failed to provide a significant increase in HDL cholesterol (1.1 mg/dL or 2.3%). This last result is surprising because numerous epidemiologic studies have shown that vitamin C intake positively correlates with HDL cholesterol concentrations.[30-34] One cross-sectional study found that a 30-mg/dL increase in plasma vitamin C concentration would result in a 3.7% to 5.0% increment in HDL cholesterol.[33] However, in interventional studies, the efficacy of vitamin C supplementation has failed to show promising results because only one of the 12 interventional studies included in this meta-analysis showed a significant positive effect. In another 2 studies, not included in this meta-analysis, vitamin C supplementation also failed to provide a positive effect upon HDL cholesterol.[35,36] One explanation for the discrepancy between the correlation and intervention studies is that plasma vitamin C levels were not elevated enough in the interventional studies to have a positive effect on HDL cholesterol. However, this does not appear to be the case because the weighted average increase in plasma vitamin C concentration for the trials entered into this meta-analysis was 46 mg/dL.

Although the magnitude of change in LDL cholesterol and triglycerides appeared modest, it can be estimated from the Atherosclerosis Risk in Communities Study[37] that an LDL cholesterol change of −7.9 mg/dL could potentially translate to a 6.6% reduction in coronary heart disease and that a change in triglycerides of −20.1 mg/dL could translate to a 2.4% reduction in coronary heart disease risk. Although the change in HDL cholesterol was not statistically significant, the 1.1-mg/dL change in HDL cholesterol could still equate to a 2.1% decrease in coronary heart disease risk. If it were possible to work out that each lipid change was mutually exclusive and played an independent mechanistic role in the future pathogenesis of coronary heart disease, then it could be surmised that vitamin C supplementation should equate to a combined decrease in coronary heart disease risk of 11.1%.

If the changes in the lipid profile established in this meta-analysis are used to determine the change in total serum cholesterol, then it could be calculated that total serum cholesterol decreased by 10.82 mg/dL (where total serum cholesterol = LDL + HDL + [triglycerides/5]). This calculated change in total serum cholesterol also happens to support the finding of a meta-analysis investigating the effects of vitamin C supplementation on total serum cholesterol that found that total serum cholesterol decreased by 10.67 mg/dL.[2] However, based upon the Atherosclerosis Risk in Communities Study[37] and the above calculated change in total serum cholesterol, this change would only equate to a decrease in coronary heart disease risk of 6.5%, which is 40% less than the coronary heart disease risk calculation of 11.1% determined in the previous paragraph. This suggests that the combined effects of vitamin C on the separate lipid profiles are not mutually exclusive or independent when generating a coronary heart disease risk score. For example, one of the protective mechanisms of HDL cholesterol is to cause inhibition of LDL oxidation.[38] Therefore, the benefits of vitamin C supplementation on increasing HDL cholesterol concentrations can indirectly carry over to act as a benefit for LDL cholesterol reduction.

It was surprising to note that the magnitude of change in triglycerides was more than doubled when compared with the change in LDL cholesterol (−20.1 vs −7.9 mg/dL, respectively). This observation is of particular interest because the literature on vitamin C mechanism and actions focuses primarily on changes in LDL and HDL cholesterol. Even reviews by Trout,[39] Simon,[40] Howard and Meyers,[41] and Lynch et al[42] had little to say about vitamin C's actions and efficacy in reducing triglycerides. However, in a review paper by Hemila on vitamin C and plasma cholesterol, he did extensively remark upon vitamin C's ability to decrease triglyceride levels.[43] By extrapolating the data from 27 groups of subjects examined in Hemila's review,[43] the weighted decrease in triglycerides was approximately 8% when compared with the control group. This finding corroborates the percentage change observed in this meta-analysis, which was 8.8%.

It has been observed that the LDL/HDL ratio is a good predictor of coronary heart disease[10]; and in this analysis, the weighted average decrease in the LDL/HDL ratio was −0.60. When compared with the control group, this equates to a 16.2% reduction from baseline. From this, it can be surmised that such a drop can translate to a 10.2% reduction in coronary

heart disease risk,[44] which is in keeping with our first predicted estimate.

The triglyceride to HDL ratio has also been shown to be a good predictor of coronary heart disease[45]; and in this analysis, the weighted average decrease in the triglyceride/HDL ratio was −0.47. When compared with the control group, this equates to a 9.4% reduction from baseline. Although the magnitude of change in the triglyceride to HDL ratio was smaller than that observed in the LDL/HDL ratio, this could still account for a similar change in coronary heart risk because it has been shown that the LDL/HDL ratio may underestimate coronary heart disease risk when compared with the estimation achieved with the triglyceride to HDL ratio.[46]

In regard to mechanism of action, it has been shown that vitamin C is able to intercept reactive oxygen species in the aqueous phase of plasma, thereby significantly reducing plasma lipid peroxide levels and thus inhibiting oxidative modification of LDLs.[47-49] This protection preserves the ability of LDL to be recognized by LDL receptors in the liver and therefore expedite its removal from the blood by LDL cholesterol catabolic pathways.[50] Vitamin C may also have a protective effect on these LDL receptors that were shown to decrease in number by approximately 25% in guinea pigs fed suboptimal vitamin C intakes.[51] This same guinea pig study also found that suboptimal vitamin C intake caused an increase in the activity of 2 cholesterol-regulating enzymes, acyl–coenzyme A: cholesterol acyltransferase and cholesterol ester transfer protein, by 20% and 30%, respectively. Increased activity of acyl–coenzyme A:cholesterol acyltransferase may result in elevated serum LDL cholesterol concentrations,[52] where an increase in cholesterol ester transfer protein activity may cause a reduction in HDL cholesterol.[53]

Vitamin C has also been shown to protect HDL cholesterol from lipid oxidation, therefore allowing it to be involved in a process known as *reverse cholesterol transport*.[54] Reverse cholesterol transport involves the removal of unesterified cholesterol from extrahepatic cell membranes to where it is esterified via lecithin: cholesterol acyltransferase. The cholesterol esters inside the HDL lipoproteins are then finally transferred back to the liver for further processing and excretion via the bile. It is known that HDL oxidation modifies apolipoprotein A-I structure, which alters the ability of the HDL lipoproteins to activate lecithin:cholesterol acyltransferase, therefore inhibiting the esterification and removal of extrahepatic cholesterol.[55,56] Most important then is the finding that vitamin C supplementation has been shown to significantly increase apolipoprotein A-I concentrations and therefore preserve the reverse cholesterol transport process.[57]

As was noted earlier, HDL lipoproteins also inhibit LDL oxidation; and this free radical scavenging effect occurs via an antioxidant enzyme called *HDL-associated paraoxonase*.[58] Vitamin C shows a capacity to prevent the loss of paraoxonase activity during oxidant stress, therefore attenuating the oxidative modification of LDL cholesterol.[59]

Vitamin C's effectiveness in reducing triglyceride concentrations was first documented in guinea pig models where a chronic borderline vitamin C deficiency led to hypertriglyceridemia.[60] It was later stated that the hypertriglyceridemia was caused by a slow uptake and removal of very low-density lipoprotein triglycerides from the plasma.[61] Vitamin C's antioxidant protection of very low-density lipoprotein may therefore facilitate its uptake by the liver and hence promote its removal from the plasma.[62,63] It has also been shown that vitamin C stimulates fatty acid utilization in hepatocytes by enhancing carnitine synthesis.[64] Carnitine is synthesized from the amino acids lysine and methionine, and vitamin C is required as a cofactor in 2 hydroxylation reactions in the pathway of carnitine biosynthesis. If increased hepatic carnitine concentration results in further hepatic fatty acid β-oxidation, then as a result, there will be a reduction in the plasma triglyceride concentration.[65,66]

In regard to the limitations of this meta-analysis, first and foremost was the pooling of clinical trials that include a considerable amount of heterogeneity in design and population characteristics. Average subject age varied between 48 and 82 years; and it is known that vitamin C concentration in serum decreases with aging, whereas a concomitant increase in total serum concentration occurs.[67] Differences in age and dietary characteristics may result in unevenly matched baseline plasma vitamin C concentrations. In the 9 groups where baseline plasma vitamin C concentrations were observed, the range varied between 28 and 75 μmol. This may confound both the starting baseline total serum cholesterol levels as well as the absorbability of vitamin C supplementation that is dependent upon initial preabsorption plasma concentrations.[15] Furthermore, not having evenly matched baseline cholesterol and triglyceride concentrations could confound the results because populations with higher concentrations could possibly exhibit a greater posttreatment effect with vitamin C supplementation. Confounders also included differences between studies in vitamin C

supplementation dose (range, 500-2000 mg/d) and study duration (range, 4-24 weeks).

Conclusion

This meta-analysis of 13 randomized controlled trials indicates that supplementation with at least 500 mg/d of vitamin C, for a minimum of 4 weeks, can result in a significant decrease in serum LDL cholesterol and triglyceride concentrations. However, there was a nonsignificant elevation of serum HDL cholesterol. Although these changes are modest, any small change can have beneficial effects on the incidence of coronary heart disease, especially in light of the low cost and absence of toxicity when supplementing vitamin C within the ranges of 500 to 1000 mg/d.[68]

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