THE EFFICACY OF VITAMIN C SUPPLEMENTATION ON REDUCING TOTAL SERUM CHOLESTEROL IN HUMAN SUBJECTS: A REVIEW AND ANALYSIS OF 51 EXPERIMENTAL TRIALS

MARC P. MCRAE MSc, DC, CNS, DACBN[a]

[a]Department of Physiology and Biochemistry, National University of Health Sciences, Lombard, IL.
Submit requests for reprints to: Dr. Marc P. McRae, National University of Health Sciences, Department of Physiology and Biochemistry, 200 East Roosevelt Rd, Lombard, Illinois, USA, 60148.
Paper submitted February 3, 2006.
Sources of support: no external funding was received for this research.

ABSTRACT

Objective: Observational studies in humans have shown an inverse relationship between plasma vitamin C concentration and total serum cholesterol. However, experimental studies have shown inconsistent results regarding the ability of vitamin C to reduce total serum cholesterol.

Methods: Published reports of trials studying the effects of vitamin C on serum lipids were identified by a search of Medline from 1966 to 2004. Data from 51 experimental studies comprising of 1666 pooled subjects were selected for analysis.

Results: A very strong negative association was observed between baseline total serum cholesterol and the percent change in cholesterol ($r = -0.585$, $p<0.001$). When subjects were divided into 4 groups based on their baseline total serum cholesterol levels, the following weighted mean percent changes in cholesterol from baseline were observed: normal cholesterol (<199mg/dl): 0.91±6.8% (n=508); borderline high cholesterol (200–239mg/dl): 3.90±5.78% (n=605); high cholesterol (240–279mg/dl): 11.40±7.96% (n=300); severe cholesterol (>280mg/dl): 14.30±8.36% (n=253). A significant inverse relationship was found between the baseline plasma vitamin C concentrations and mean percent change in total cholesterol from baseline ($r = -0.500$, $p<0.005$). It was also observed that the high and severe baseline cholesterol groups possessed lower baseline plasma vitamin C concentrations than those in the normal cholesterol groups (0.79 and 0.55 versus 1.24 mg/dl respectively).

Conclusion: This finding strengthens the hypothesis that the cholesterol lowering and cardio-protective benefit of vitamin C supplementation may be in its ability to elevate plasma vitamin C concentrations in those patients who initially possess lower than normal vitamin C plasma concentrations. (J Chiropr Med 2006;5:2–12)

Key Indexing Terms: Ascorbic Acid; Cholesterol

INTRODUCTION

Heart disease is the leading cause of premature death and disability in the United States. Hypercholesterolemia is a primary risk factor leading to coronary heart disease and the American Heart Association estimates approximately 42 million American adults have total serum cholesterol levels of greater than 240 mg/dL.[1] Over the past decades a number of nutritional compounds have shown some promise in reducing plasma cholesterol concentrations. One such compound is vitamin C. Animal studies have shown that vitamin C participates in cholesterol metabolism, and that a marginal vitamin C deficiency increases plasma cholesterol concentrations.[2] Observational studies using human populations have shown an inverse relationship between vitamin C intake and mortality due to cardiovascular disease.[3,4] However cross-sectional and longitudinal studies examining the relationship between total serum cholesterol and vitamin C have shown conflicting and inconclusive results.[5,6] Furthermore experimental studies have also shown inconsistent results regarding the ability of vitamin C to reduce total serum cholesterol.[7,8] In a review by Howard and Meyers in 1995 on the effects of vitamin C and its efficacy in reducing total serum cholesterol, the authors concluded that vitamin C supplementation for preventing hypercholesterolemia should not be recommended.[9]

However, on closer examination, several of the past experimental trials have utilized subjects with ini-

0899-3467/06/1002-049$3.00/0
JOURNAL OF CHIROPRACTIC MEDICINE
Copyright © 2006 by National University of Health Sciences

tially low baseline total serum cholesterol concentrations, and therefore very few of these studies have shown any decrease in total cholesterol with vitamin C supplementation.[10] Moreover, the majority of experimental studies using hypercholesterolemic subjects have illustrated significant decreases in total cholesterol concentrations.[11] This finding is significant since there is a strong independent relationship between total serum cholesterol and long-term risk of coronary heart disease and cardiovascular death.[12] The purpose of this review is to analyze published experimental trials in order to identify if vitamin C supplementation would truly be effective in patients with high unfavorable total serum cholesterol levels (greater than 240mg/dl).

METHODS

Using MEDLINE (January 1966 through December 2004) all published studies involving human subjects that evaluated the effects of vitamin C on total serum lipids were obtained using the terms ["Vitamin C" OR "Ascorbic Acid"] AND ["Cholesterol" OR "Lipids"]. All studies identified as experimental trials were retrieved for analysis and additional publications were identified from the bibliographies of previously retrieved papers. Data was extracted from the published reports and the following items were entered into an Excel spreadsheet: study design; number of subjects; mean age or age range; vitamin C dose/day; duration of treatment; baseline and post treatment measures of total serum cholesterol and plasma vitamin C.

Correlation coefficients were calculated for baseline total serum cholesterol and baseline plasma vitamin C versus the percent change in cholesterol. As well all studies were stratified among 4 categories based upon their mean baseline total serum cholesterol levels: Normal total serum cholesterol: <199 mg/dl; Borderline-High: 200 to 239 mg/dl; High: 240 to 280 mg/dl; and Severe: >280 mg/dl. Within each baseline total cholesterol category the populations from each study were pooled and weighted mean changes from baseline for total serum cholesterol and plasma vitamin C were compared. Comparisons were not statistically analyzed because the standard deviation of weighted means did not reflect between-subject variances, but only between-study variances.

RESULTS

Fifty experimental trials[3,7,8,13–60] comprised of 1666 pooled subjects were retrieved and entered into Tables 1–4 with respect to their baseline total serum cholesterol. A very strong negative association was observed in Figure 1 between baseline total serum cholesterol and the percent change in cholesterol. The correlation coefficient was negative 0.585 and this was significant (p=.000). A negative association between baseline plasma vitamin C concentration and the change in total serum cholesterol was observed in Figure 2 and also found to be significant (p=.003). The correlation coefficient observed in Figure 2 was negative 0.500. A change in plasma vitamin C was subsequently compared against the change in total serum cholesterol, and there was clearly no observable association (correlation coefficient was 0.007, Fig 3).

After the studies were separated into 4 categories based on their baseline total serum cholesterol concentrations, it was observed that the very high baseline cholesterol group started out with the lowest plasma vitamin C levels and obtained the highest mean percent change in total serum cholesterol when compared to the other 3 groups. These results and comparisons can be observed in Tables 5 and 6.

DISCUSSION

When subjects are supplemented with vitamin C a significant inverse relationship is observed between baseline and the mean percent change in total serum cholesterol. A similar but even stronger correlation coefficient of -0.86 was observed by Hemila in 1992.[10] However, this observation was based only upon 12 vitamin C experimental trials. Based on the data compiled in this review it can be predicted from the linear regression lines that subjects with total serum cholesterol concentrations ≥270mg/dl should expect a decrease of at least 10% in the total serum cholesterol levels. This review does not fully support the conclusion of Howard and Meyers[9] that suggests that vitamin C not be recommended for the treatment of hypercholesterolemia. This contradictory finding is supported by the fact that experimental trials using patient populations with total serum cholesterol levels >280mg/dl observed a 14% decrease in total serum cholesterol.

For severe hypercholesterolemic populations (>280mg/dl), vitamin C is able to achieve comparable decreases in total serum cholesterol when compared to other nutritional supplements: pantethine (14.9%); niacin (12.4%); garlic (9.0%).[61]

TABLE 1
SUMMARY OF TRIALS INVESTIGATING THE EFFECT OF VITAMIN C ON TOTAL SERUM CHOLESTEROL IN SUBJECTS WITH NORMAL BASELINE TOTAL SERUM CHOLESTEROL (LESS THAN 200 MG/DL).

						Total Serum Cholesterol		Plasma Vitamin C	
Author and Year [Ref]	Study Design*	Sample Size	Mean Age	Duration (weeks)	Dose Vitamin C/day (mg)	Baseline (mg/dl)	Change from Baseline (%)	Baseline (mg/dl)	Change from Baseline (mg/dl)
Spittle 1971 [14]	BC	20	20–25	6	1000	194	−8.76		
Crawford et al. 1975 [15]	R,SB	17	24.9	12	1000	185	4.86		
Menne et al. 1975 [16]	R,SB	62	18–25	16	1000	175	9.14	1.31	0.43
Kallner 1977 [22]	BC	14	<25	4	5000	186.49	3.31	1.39	0.41
Vijayakumar and Vasudevan 1980 [29]	BC	10	30–45	2	3000	198.8	−6.19		
Vijayakumar and Vasudevan 1980 [29]	BC	20	30–45	2	3000	189.1	−5.71		
Horsey et al. 1981 [30]	BC	14	81.8	6	1000	178.76	5.62		
Johnson and Obenshain 1981 [31]	SB,PCO	9	23–36	6	1000	165.6	5.13	1.31	0.15
Josi et al. 1981 [32]	BC	27	17–20	3	2000	163	14.11		
Khan and Seedarnee 1981 [33]	BC	13	22.5	4	1000	176.5	−0.74	1.06	0.29
Buzzard et al. 1982 [34]	SB,PC	10	25.3	6	2000	156.8	−0.26	1.37	0.45
O'Brien and McMurray 1988 [44]	BC	20	36–60	12	1500	197	−1.52	0.99	0.49
Beser 1991 [45]	SB,PCO	105	20	4	500	169.72	−10.34	1.19	1.12
Osilesi et al. 1991 [46]	SB,PCO	20	57.8	6	1000	194.59	−0.59	1.44	0.06
Eriksson and Kohvakka 1995 [50]	R,DB,PC	29	43	12	2000	196.91	−1.96		
Jacques et al. 1995 [3]	R,SB,PC	74	41	32	1000	188.03	2.88	1.27	1.04
Gatto et al. 1996 [52]	R,DB,PCO	10	22.1	4	1000	195.75	−9.86	1.08	0.8
Samman et al. 1997 [55]	SB,PCO	8	25.3	2	1000	176.45	0.22	0.96	1
Tofler et al. 2000 [58]	R,DB,PCO	18	40	6	2000	184	−9.24	1.39	0.89
Martinez-Abundis et al. 2001 [59]	R,DB,PC	8	26.1	4	1000	192.5	−8.26		

* BC (Baseline Comparison); R (Randomized); DB (Double Blind); SB (Single Blind); PC (Placebo Control); PCO (Placebo Cross Over).

Even more encouraging is that vitamin C can be supplemented up to 2 grams/day without any serious side effects.[62,63] Patients supplementing with niacin have complained of a number side effects which have included flushing and pruritis[64], while patients supplementing with garlic have been observed to complain of headaches, nausea, heartburn and garlic odor.[65]

A significant inverse relationship was observed between baseline plasma vitamin C concentrations and baseline total serum cholesterol concentrations. Therefore, a population with marginal vitamin C status combined with elevated serum cholesterol may benefit from vitamin C supplementation. However the absolute increase in plasma vitamin C concentration post treatment was similar for all groups,

TABLE 2
SUMMARY OF TRIALS INVESTIGATING THE EFFECT OF VITAMIN C ON TOTAL SERUM CHOLESTEROL IN SUBJECTS WITH BORDERLINE-HIGH BASELINE TOTAL SERUM CHOLESTEROL (BETWEEN 200–239.9 MG/DL).

						Total Serum Cholesterol		Plasma Vitamin C	
Author and Year [Ref]	Study Design*	Sample Size	Mean Age	Duration (Weeks)	Dose Vitamin C/day (mg)	Baseline (mg/dl)	Change from Baseline (%)	Baseline (mg/dl)	Change from Baseline (mg/dl)
Spittle 1971 [14]	BC	19	25–45	6	1000	207	3.86		
Spittle 1971 [14]	BC	19	45–60	6	1000	236	0.00		
Pedersen 1975 [18]	BC	10		2	1000	223.94	–5.17		
Ginter et al. 1977 [20]	BC	82	64	12	1000	207	–5.31		
Hanck and Weiser 1977 [21]	BC	10	25–45	3	4000	213.3	–8.67	1.03	0.53
Kothari and Jain 1977 [23]	R,SB	10	20–30	4	1000	204	–13.24	0.76	0.48
Fidanza et al. 1979 [24]	BC	12	65–90	3	3000	225	–13.78	0.91	0.19
Horsey et al. 1981 [30]	BC	11	81.8	6	1000	201.16	–0.58		
Fidanza et al. 1982 [35]	BC	20	44–79	3	3000	225	–13.78		
Dobson et al. 1984 [37]	BC	12	29	24	1000	227.8	–16.95	0.85	0.37
Kho 1984 [38]	BC	23	>35	12	1000	239	–9.62	1.58	0.27
Erden et al. 1985 [40]	BC	25	21	8	2000	200.12	–8.08		
Aro et al. 1988 [41]	DB,PCO	27	81	6	2000	206.95	0.56	0.424	1.776
Salonen et al. 1991 [47]	R,DB,PC	39	54	20	600	216.22	–1.79	0.5	0.83
Munoz et al. 1994 [49]	R,SB,PCO	124	17–74	4	1000	200.7	–1.05		
Eriksson and Kohvakka 1995 [50]	R,DB,PCO	27	61	12	2000	239.38	–4.84		
Gustafsson et al. 1997 [53]	BC	13	52	2	2000	216.22	–1.79	1.22	0.51
Gokce et al. 1999 [54]	R,DB,PCO	21	56	4	500	207	–1.93		
Fotherby et al. 2000 [56]	R,DB,PCO	40	72	12	500	239.38	0.00	0.86	0.64
Hamilton et al. 2000 [57]	R,DB,PCO	30	35	6	500	206.95	–6.16	1.11	0.67
Singhal et al. 2001 [8]	R,SB,PC	31	54.7	4	1000	207.4	–1.49		

* BC (Baseline Comparison); R (Randomized); DB (Double Blind); SB (Single Blind); PC (Placebo Control); PCO (Placebo Cross Over).

regardless of their pre-plasma vitamin C status. For all 3 hypercholesterolemic groups their baseline plasma vitamin C concentrations were taken beyond the average concentrations typically seen in normocholesterolemic subjects. The severe cholesterol group experienced the greatest increase in plasma vitamin C levels and this may be explained by the fact that they started out with the lowest baseline values and/or their median dosage of vitamin C was 2000mg/day as compared to the 1000mg/day with the other groups. The results observed here lead us to ask whether there is a cut off level for plasma vitamin C concentrations in which subjects who are below this level show deficiencies in cholesterol metabolism?

If low plasma vitamin C concentrations are to blame for the high total serum cholesterol levels, then where in cholesterol metabolism does vitamin C play out its function? It was originally believed that

TABLE 3
SUMMARY OF TRIALS INVESTIGATING THE EFFECT OF VITAMIN C ON TOTAL SERUM CHOLESTEROL IN SUBJECTS WITH HIGH BASELINE TOTAL SERUM CHOLESTEROL (BETWEEN 240–279.9 MG/DL).

						Total Serum Cholesterol		Plasma Vitamin C	
Author and Year [Ref]	Study Design*	Sample Size	Mean Age	Duration (Weeks)	Dose Vitamin C/day (mg)	Baseline (mg/dl)	Change from Baseline (%)	Baseline (mg/dl)	Change from Baseline (mg/dl)
Ginter et al. 1970 [13]	BC	24	42–65	7	300	255	−6.67		
Spittle 1971 [14]	BC	25	54	6	1000	242	7.85		
Ginter 1975 [17]	BC	24	62.5	24	1000	253	−17.00		
Ginter et al. 1977 [20]	BC	19	62	48	1000	263	−12.93	0.61	0.81
Kothari and Jain 1977 [23]	R,SB	10	30–40	4	1000	256	−12.11	0.74	0.48
Filho et al. 1978 [25]	BC	19	75	2	2000	272.1	−25.15		
Dobson et al. 1984 [37]	BC	10	58	24	2000	270.27	−14.29	1.03	1.07
Bishop et al. 1985 [39]	R,DB,PCO	50	55.7	8	500	270.27	−5.71	0.73	0.9
Gulenc and Nebioglu 1998 [42]	BC	38		8	2000	264.97	−16.04	0.75	0.11
Mamianetti et al. 1988 [43]	BC	14	48.5	3	1500	250.57	−8.81		
Paolisso et al. 1995 [51]	R,DB,PCO	40	72	16	1000	278	−19.45	0.72	0.61
Vinson and Jang 2001 [7]	R,DB,PC	10	53	8	1000	279.15	−8.30		
Shidfar et al. 2003 [60]	R,DB,PC	17	51.8	10	500	243.5	−10.68	1.32	0.3

* BC (Baseline Comparison); R (Randomized); DB (Double Blind); SB (Single Blind); PC (Placebo Control); PCO (Placebo Cross Over).

vitamin C's cholesterol lowering effects was due to its role as a cofactor for the enzyme 7-alpha-hydroxylase, the rate limiting enzyme in the transformation of cholesterol to bile acids.[66] However this hypothesis has been disconfirmed in subsequent research which showed that plasma vitamin C concentrations had no effect on the rates of bile acid production in the liver.[53,67] Therefore vitamin C might play out its role in the mechanisms responsible for the removal of cholesterol from the blood. In one study it was observed that there was a vitamin C dependent increase in the activity of lecithin cholesterol acyltransferase (LCAT).[21,68] LCAT is involved in the mechanism of reverse cholesterol transport by which it is responsible for the esterification of extrahepatic free cholesterol and its sequestration into the core of high density lipoproteins (HDL). This subsequently leads to the selective transfer of cholesterol from the peripheral cells back to the liver and therefore elevates the rate of cholesterol turnover and decreases total serum cholesterol levels. It has also been shown that vitamin C may be able to increase the number of LDL receptors which would increase the catabolic rate of LDL-cholesterol and its removal from the blood.[69] These may be the mechanisms by which to explain why lower than optimal plasma vitamin C concentrations leads to observable elevations of total serum cholesterol.

Recently it has been shown that disturbances in serum pro-oxidant-antioxidant balance as well as an increase in low density lipoprotein (LDL) oxidation are concomitant with higher total serum cholesterol levels.[70] These findings support evidence suggesting that the hypocholesterolemic effects of vitamin C may be due to its antioxidant ability.[71,72] Vitamin C has been shown to significantly reduce lipid peroxide levels[8] and protect LDL cholesterol from oxidation, thus facilitating LDL's normal binding to membrane receptors on the liver and therefore expedite its removal from the blood by LDL-cholesterol catabolic pathways.[73] However, a couple of groups contest this finding as they observed that vitamin C did not protect plasma lipids[74] or LDL[7,75] from oxidation, and one group suggested that this is because

TABLE 4
SUMMARY OF TRIALS INVESTIGATING THE EFFECT OF VITAMIN C ON TOTAL SERUM CHOLESTEROL IN SUBJECTS WITH SEVERE BASELINE TOTAL SERUM CHOLESTEROL (GREATER THAN 280 MG/DL).

						Total Serum Cholesterol		Plasma Vitamin C	
Author and Year [Ref]	Study Design*	Sample Size	Mean Age	Duration (Weeks)	Dose Vitamin C/day (mg)	Baseline (mg/dl)	Change from Baseline (%)	Baseline (mg/dl)	Change from Baseline (mg/dl)
Peterson et al. 1975 [19]	BC	9	46	8	4000	304	2.30	0.49	1.71
Fidanza et al. 1978 [24]	BC	14	65–90	3	3000	290	−14.14	0.86	0.09
Ginter et al. 1978 [26]	DB,PC	35	50–60	12	500	337	−19.88	0.35	0.55
Heine and Norden 1979 [27]	BC	63	57.3	48	1000	329.6	−11.13		
Bordia 1980 [28]	R,DB,PC	20	50.8	24	2000	285	−12.28	0.5	0.47
Fidanza et al. 1982 [35]	BC	20	63.1	3	3000	311.8	−18.02		
Wahlberg and Walldius 1982 [36]	SB,PCO	9	55	4	2000	287.26	0.54		
Cerna et al. 1992 [48]	BC	83	48	18	500	295.75	−17.36	0.6	1.14

* BC (Baseline Comparison); R (Randomized); DB (Double Blind); SB (Single Blind); PC (Placebo Control); PCO (Placebo Cross Over).

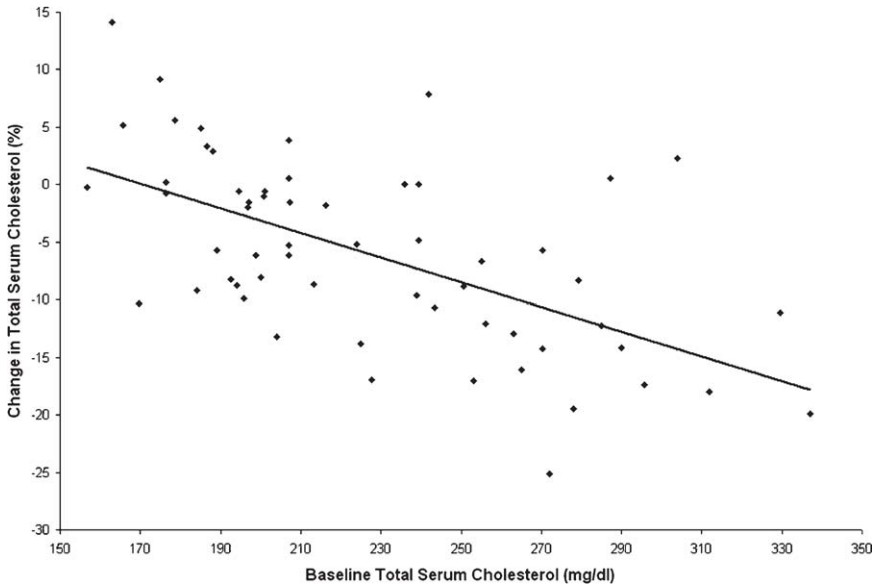

Figure 1. Percent change in total serum cholesterol versus baseline total serum cholesterol.

vitamin C is hydrophilic and does not bind to lipoproteins.[7] Yet another group countered this point and suggested that vitamin C is able to protect polyunsaturated fatty acids from oxidation and thereby limit the concentration oxidative byproducts, such as malondialdehyde, which function to inhibit normal LDL catabolism.[60] If the mechanism by which vitamin C exerts its effects on cholesterol metabolism is via its antioxidative role on LDL cholesterol, then it should be observed that other antioxidants may also play a role in reducing total serum cholesterol. However, examination of the lipid lowering effects of other well known antioxidants such as vitamin E,[8,76–80] vitamin A,[8] beta-carotene,[81] lyco-

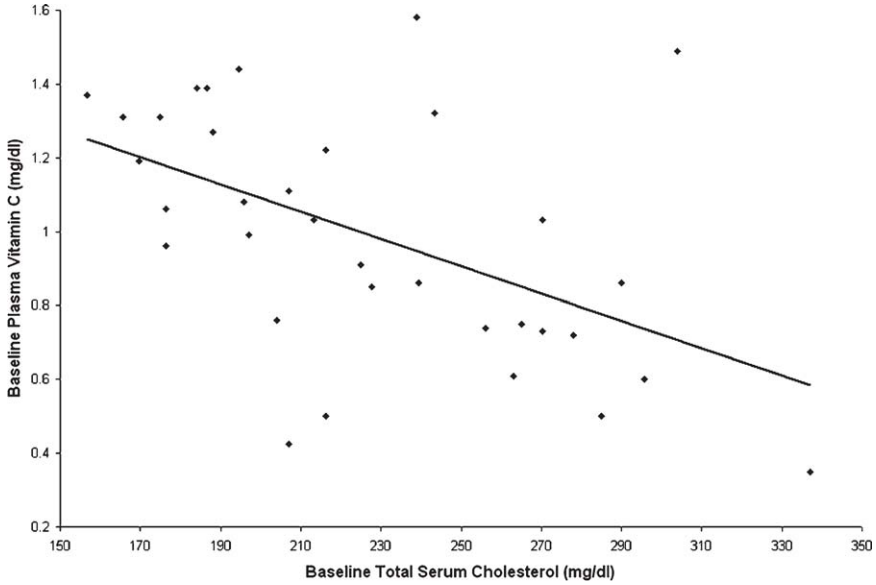

Figure 2. Association between baseline plasma vitamin C and baseline total serum cholesterol.

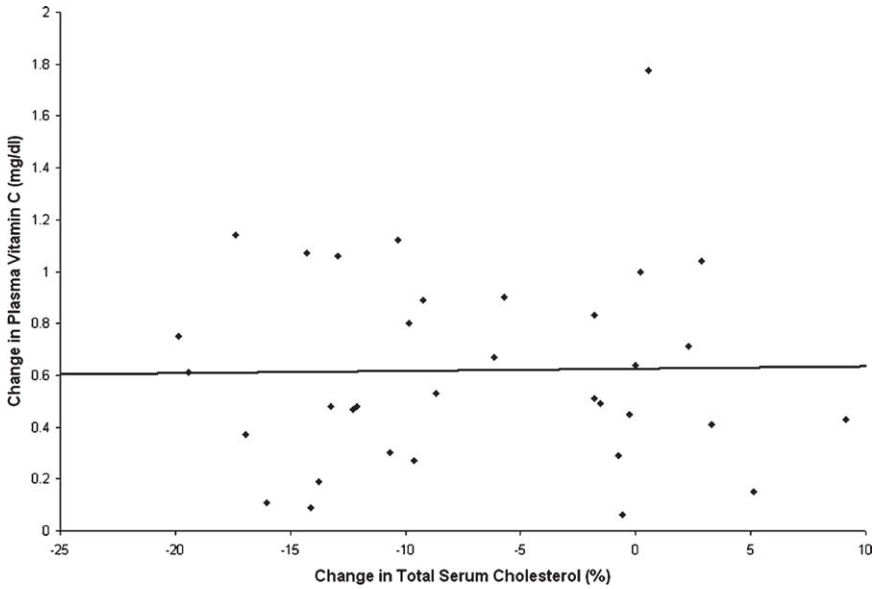

Figure 3. Changes in plasma vitamin C concentration versus changes in total serum cholesterol concentration.

pene,[82] and coenzyme Q10[83] have all failed to provide support for this proposed mechanism. However a study on gamma-oryzanol, extracted from rice bran, found this compound able to significantly reduce cholesterol oxidation and the authors suggested that this may contribute to the potential hypocholesterolemic property of rice bran.[84]

Although the underlying mechanisms are not yet fully understood, it is reasonable to assume that the hypocholesterolemic properties of vitamin C are most profound when total serum cholesterol is greater than 240mg/dl. However these effects may be limited to a subset of the population who possess an underlying vitamin C deficiency and therefore only certain groups of hypercholesterolemic subjects could potentially benefit from vitamin C supplementation. For example, in some groups of elderly people the mean vitamin C level was found to be below 0.3 mg/dl which may lead to their substan-

TABLE 5
CHARACTERISTICS OF THE VITAMIN C EXPERIMENTAL STUDIES AND CHANGES IN TOTAL SERUM CHOLESTEROL FROM BASELINE (SD).

Total Serum Cholesterol Baseline Stratum (mg/dl)	No. Studies/ No. Pooled Subjects	Mean Age	Median Vitamin C Dose (mg)	Median Study Duration (Weeks)	Weighted Baseline Total Serum Cholesterol (mg/dl)	Weighted End Point Total Cholesterol (mg/dl)	Weighted Percentage Mean Change From Baseline	Ratio of Studies Observing Statistical Significance
150 to 199	20/508	27.3 (18.5)	1000	6	181.1 (12.5)	179.4 (12.4)	0.91 (6.8)	5/20
200 to 239	21/605	37.9 (20.1)	1000	6	213.8 (13.8)	205.3 (16.5)	3.90 (5.78)	8/21
240 to 279	13/300	42.8 (8.7)	1000	8	262.7 (12.4)	232.2 (17.5)	11.40 (7.96)	10/13
>280	8/253	52.8 (6.4)	2000	8	310.0 (19.6)	265.5 (24.7)	14.30 (8.36)	6/8

TABLE 6
CHANGES IN PLASMA VITAMIN C ACROSS BASELINE TOTAL CHOLESTEROL CATEGORIES (SD).

Total Serum Cholesterol Baseline Stratum (mg/dl)	No. Pooled Subjects	Weighted Baseline Plasma Vitamin C (mg/dl)	Weighted End Point Plasma Vitamin C (mg/dl)	Weighted Mean Change in Plasma Vitamin C (mg/dl)
150 to 199	363	1.24 (0.17)	2.01 (0.34)	0.77 (0.36)
200 to 239	216	0.88 (0.34)	1.60 (0.34)	0.72 (0.45)
240 to 279	184	0.79 (0.25)	1.39 (0.39)	0.60 (0.34)
>280	161	0.55 (0.19)	1.42 (0.59)	0.87 (0.64)

tially higher total serum cholesterol levels.[20,85] This may explain why in this review the severe hypercholesterolemic group possessed the largest percent change in total serum cholesterol from baseline as this group was made up of a significantly older population which possessed the lowest baseline plasma vitamin C levels (0.55 mg/dl) when compared to the other 3 groups.

There is considerable uncertainty about the optimal level of vitamin C intake, and it is widely believed that the greater the amount consumed the greater the beneficial effect in terms of preventing coronary heart disease. However, it has been observed that plasma concentrations of vitamin C are completely saturated at doses of 400 mg daily and higher, producing a steady state plasma concentration of approximately 1.40 mg/dl in both males and females.[86,87] This finding is somewhat interesting in light of the fact that all but one of the studies in this review utilized doses of vitamin C that were greater than 400mg/day, and that the post experimental plasma concentrations for a majority of the groups (2 of every 3) exceeded 1.40 mg/dl. In normal healthy populations, which were used in these plasma saturation studies, it appears that 400mg/day of vitamin C is adequate for plasma saturation. But for an elderly hypercholesterolemic population who may possibly possess a chronic vitamin C plasma concentration deficiency, it may be possible that 400mg/day is not sufficient to obtain saturated plasma levels and hence reach full vitamin C tissue saturation. Tissue concentrations of vitamin C usually exceed plasma concentrations, with the magnitude dependent on the specific tissue.[86] Because individuals with less than full vitamin C tissue saturation possess elevated cholesterol levels[11] it would therefore appear that vitamin C doses of greater than 400mg/day may be required to sufficiently obtain tissue and plasma saturation leading to the anti-hypercholesterolemic effects seen in these high to sever hypercholesterolemic patient populations.

Although having high total serum cholesterol is considered a major risk factor for developing cardiovascular disease, supplementing with vitamin C at doses of greater than 400mg/day may be efficacious as vitamin C has been shown to possess other well documented cardio-protective qualities beyond just reducing total serum cholesterol.[11] In a pooled analysis of 9 cohort studies subjects who took greater than 700mg supplemental vitamin C intake per day had a lower incidence of coronary heart disease compared with subjects who did not take supplemental vitamin C.[88]

This review includes some limitations such that the comparisons made across stratum of baseline total

serum cholesterol are based on an extremely heterogeneous population of experimental trials. Also, the validity of many of these experimental trials are in question, because of the lack of randomized treatment allocations, failure to blind treatment, small sample sizes, short treatment durations and the considerably large range of vitamin C dosage used which spanned between 300 to 5000mg per day. The majority of these experimental trials tended to suffer from serious research design flaws as only 6 of the 51 trials used a randomized double-blind placebo-controlled parallel research design. It is because of this small number of randomized control trials that this current review used a pooled analysis and descriptive approach as opposed to a meta-analysis design.

CONCLUSIONS

It has been shown that total serum cholesterol levels at baseline can predict long-term cardiovascular mortality.[89] Therefore daily supplementation of a minimum of 400mg of vitamin C for the more than 42 million Americans with total serum cholesterol levels of greater than 240 mg/dl may possess substantial public health benefits. The benefit appears to be most pronounced in patients with severe hypercholesterolemia (total serum cholesterol greater than 280mg/dl) who in combination possess plasma vitamin C concentrations of less than 0.6mg/dl. However these findings are constrained by the fact that there are not enough well-constructed studies. Therefore further randomized, double-blind, placebo-controlled trials are needed to support the efficacy of vitamin C supplementation with high to severe hypercholesterolemic patients. It would be of immense value if these studies are conducted using a large sample size of hypercholesterolemic patients who concomitantly possess low plasma vitamin C levels.

REFERENCES

1. American Heart Association. Heart disease and stroke statistics—2003 update. Dallas: American Heart Association; 2002.
2. Freyschuss A, Xiu RJ, Zhang J, et al. Vitamin C reduces cholesterol-induced microcirculatory changes in rabbits. Arterioscler Thromb Vasc Biol 1997 Jun;17:1178–84.
3. Jacques PF, Sulsky SI, Perrone GE, Jenner J, Schaefer EJ. Effect of vitamin C supplementation on lipoprotein cholesterol, apolipoprotein, and triglyceride concentrations. Ann Epidemiol 1995;5:52–9.
4. Simon JA, Hudes ES. Relation of serum ascorbic acid to serum lipids and lipoproteins in US adults. J Am Coll Nutr 1998;17:250–5.
5. Ness AR, Khaw KT, Bingham S, Day NE. Vitamin C status and serum lipids. Eur J Clin Nutr 1996;50:724–9.
6. Kim MK, Sasaki S, Sasazuki S, Okubo S, Hayashi M, Tsugane S. Long-term vitamin C supplementation has no markedly favourable effect on serum lipids in middle-aged Japanese subjects. Br J Nutr 2004; 91:81–90.
7. Vinson JA, Jang J. In vitro and in vivo lipoprotein antioxidant effect of a citrus extract and ascorbic acid on normal and hypercholesterolemic human subjects. J Med Food 2001;4:187–92.
8. Singhal S, Gupta R, Goyle A. Comparison of antioxidant efficacy of vitamin E, vitamin C, vitamin A and fruits in coronary heart disease: a controlled trial. J Assoc Physicians India 2001; 49:327–31.
9. Howard PA, Meyers DG. Effect of vitamin C on plasma lipids. Ann Pharmacother 1995;29:1129–36.
10. Hemila H. Vitamin C and plasma cholesterol. Crit Rev Food Sci Nutr 1992;32:33–57.
11. Simon JA. Vitamin C and cardiovascular disease: a review. J Am Coll Nutr 1992;11:107–25.
12. Stamler J, Daviglus ML, Garside DB, Dyer AR, Greenland P, Neaton JD. Relationship of baseline serum cholesterol levels in 3 large cohorts of younger men to long-term coronary, cardiovascular, and all-cause mortality and to longevity. JAMA 2000;284:311–8.
13. Ginter E, Kajaba I, Nizner O. The effect of ascorbic acid on cholesterolemia in healthy subjects with seasonal deficit of vitamin C. Nutr Metab 1970;2:76–86.
14. Spittle CR. Atherosclerosis and vitamin C. Lancet 1971;2:1280–1.
15. Crawford GP, Warlow CP, Bennett B, et al. The effect of vitamin C supplements on serum cholesterol, coagulation, fibrinolysis and platelet adhesiveness. Atherosclerosis 1975;21:451–4.
16. Menne IV, Grey PC, Kotze JP, Sommers DK, Brown JM, Spies JH. Ascorbic acid and blood lipid and uric acid levels of students. S Afr Med J 1975;49:2225–8.
17. Ginter E. Ascrobic acid in cholesterol and bile acid metabolism. Ann NY Acad Sci 1975;258:410–21.
18. Pedersen L. Biliary lipids during vitamin C feeding in healthy persons. Scand J Gastroent 1975;10:311–4.
19. Peterson VE, Crapo PA, Weininger J, Ginsberg H, Olefsky J. Quantification of plasma cholesterol and triglyceride levels in hypercholesterolemic subjects receiving ascorbic acid supplements. Am J Clin Nutr 1975;28:584–7.
20. Ginter E, Cerna O, Budlovsky J, et al. Effect of ascorbic acid on plasma cholesterol in humans in a long-term experiment. Int J Vitam Nutr Res 1977;47:123–34.
21. Hanck A, Weiser H. Vitamin C and lipid metabolism. Int J Vitam Nutr Res 1977; Suppl 16:67–81.
22. Kallner A. Serum bile acids in man during vitamin C supplementation and restriction. Acta Med Scand 1977;202:283–7.
23. Kothari LK, Jain K. Effect of vitamin C administration on blood cholesterol level in man. Acta Biol 1977;28:111–4.
24. Fidanza A, Floridi S, Martinoli L, et al. Therapeutic action of vitamin C on cholesterol metabolism. Boll Soc Ital Biol Sper 1979;55:553–8.
25. Filho RL, Lima MB, Kneipp R, Cunha LC, Ogliari M. Alteracoes dos niveis sericos de cholesterol, em pacientes sob o uso de acido ascorbico. Folha Medica 1978;77:451–4.
26. Ginter E, Zdichynec B, Holzerova O, et al. Hypocholesterolemic effect of ascorbic acid in maturity-onset diabetes mellitus. Int J Vitam Nutr Res 1978;48:368–73.
27. Heine H, Norden C. Vitamin C therapy in hyperlipoproteinemia. Int J Vitam Nutr Res 1979;Suppl 19:45–54.
28. Bordia AK. The effect of vitamin C on blood lipids, fibrinolytic activity and platelet adhesiveness in patients with coronary artery disease. Atherosclerosis 1980;35:181–7.
29. Vijayakumar T, Vasudevan DM. Effect of ascorbic acid administration on glucose tolerance and serum cholesterol in normal and in diabetic subjects. Ind Med Gaz 1980:96–100.
30. Horsey J, Livesley B, Dickerson JW. Ischaemic heart disease and aged patients: effects of ascorbic acid on lipoproteins. J Hum Nutr 1981; 35:53–8.
31. Johnson GE, Obenshain SS. Nonresponsiveness of serum high-density lipoprotein-cholesterol to high dose ascorbic acid administration in normal men. Am J Clin Nutr 1981;34:2088–91.
32. Joshi VD, Joshi LN, Gokhale LV. Effect of ascorbic acid on total and high density lipoprotein cholesterol of plasma in normal human subjects. Indian J Physiol Pharmacol 1981;25:348–50.
33. Khan AR, Seedarnee FA. Effect of ascorbic acid on plasma lipids and

lipoproteins in healthy young women. Atherosclerosis 1981;39: 89–95.
34. Buzzard IM, McRoberts MR, Driscoll DL, Bowering J. Effect of dietary eggs and ascorbic acid on plasma lipid and lipoprotein cholesterol levels in healthy young men. Am J Clin Nutr 1982;36:94–105.
35. Fidanza A, Audisio M, Mastroiacovo P. Vitamin C and cholesterol. Int J Vitam Nutr Res Suppl 1982;23:153–71.
36. Wahlberg G, Walldius G. Lack of effect of ascorbic acid on serum lipoprotein concentrations in patients with hypertriglyceridaemia. Atherosclerosis 1982;43:283–8.
37. Dobson HM, Muir MM, Hume R. The effect of ascorbic acid on the seasonal variations in serum cholesterol levels. Scott Med J 1984;29: 176–82.
38. Koh ET. Effect of vitamin C on blood parameters of hypertensive subjects. J Okla State Med Assoc 1984;77:177–82.
39. Bishop N, Schorah CJ, Wales JK. The effect of vitamin C supplementation on diabetic hyperlipidaemia: a double blind, crossover study. Diabet Med 1985;2:121–4.
40. Erden F, Gulenc S, Torun M, Kocer Z, Simsek B, Nebioglu S. Ascorbic acid effect on some lipid fractions in human beings. Acta Vitaminol Enzymol 1985;7:131–7.
41. Aro A, Kyllastinen M, Kostiainen E, Gref CG, Elfving S, Uusitalo U. No effect on serum lipids by moderate and high doses of vitamin C in elderly subjects with low plasma ascorbic acid levels. Ann Nutr Metab 1988;32:133–7.
42. Gulenc S, Nebioglu S. Oral yolla askorbik asit alan kisilerde sigara kullanimmina bagli serum trigliserit, total kolesterol ve HDL-kolesterol duzeyleri. FABAD J Pharm Sci 1988;13:493–99.
43. Mamianetti A, Vescina MC, Matejka MA, Alvarez O, Dameno E, Carducci CN. Efecto del acido ascorbico sobre los lipidos biliares en pacientes litiasicos. Prensa Med Argent 1988;75:346–50.
44. O'Brien BC, McMurray DN. Human plasma lipid and immunologic responses to eggs and ascorbic acid. Nut Res 1988;8:353–66.
45. Beser E. The effects of short-term vitamin C on plasma bun, uric acid, cholesterol and triglyceride levels. Acta Med Hung 1991;48:73–8.
46. Osilesi O, Trout DL, Ogunwole JO, Glover EE. Blood pressure and plasma lipids during ascorbic acid supplementation in borderline hypertensive and normotensive adults. Nut Res 1991;11:405–12.
47. Salonen JT, Salonen R, Seppanen K, et al. Effects of antioxidant supplementation on platelet function: a randomized pair-matched, placebo-controlled, double-blind trial in men with low antioxidant status. Am J Clin Nutr 1991;53:1222–9.
48. Cerna O, Ramacsay L, Ginter E. Plasma lipids, lipoproteins and atherogenic index in men and women administered vitamin C. Cor Vasa 1992;34:246–54.
49. Munoz JA, Garcia C, Quilez JL, Andugar MA. Effect of vitamin C on lipoproteins in healthy adults. Ann Med Interne (Paris) 1994;145: 13–9.
50. Eriksson J, Kohvakka A. Magnesium and ascorbic acid supplementation in diabetes mellitus. Ann Nutr Metab 1995;39:217–23.
51. Paolisso G, Balbi V, Volpe C, et al. Metabolic benefits deriving from chronic vitamin C supplementation in aged non-insulin dependent diabetics. J Am Coll Nutr 1995;14:387–92.
52. Gatto LM, Hallen GK, Brown AJ, Samman S. Ascorbic acid induces a favorable lipoprotein profile in women. J Am Coll Nutr 1996;15: 154–8.
53. Gustafsson U, Wang FH, Axelson M, Kallner A, Sahlin S, Einarsson K. The effect of vitamin C in high doses on plasma and biliary lipid composition in patients with cholesterol gallstones: prolongation of the nucleation time. Eur J Clin Invest 1997;27:387–91.
54. Gokce N, Keaney JF, Frei B, et al. Long-term ascorbic acid administration reverses endothelial vasomotor dysfunction in patients with coronary artery disease. Circulation 1999;99:3234–40.
55. Samman S, Brown AJ, Beltran C, Singh S. The effect of ascorbic acid on plasma lipids and oxidisability of LDL in male smokers. Eur J Clin Nutr 1997;51:472–7.
56. Fotherby MD, Williams JC, Forster LA, Craner P, Ferns GA. Effect of vitamin C on ambulatory blood pressure and plasma lipids in older persons. J Hypertens 2000;18:411–5.
57. Hamilton IM, Gilmore WS, Benzie IF, Mulholland CW, Strain JJ. Interactions between vitamins C and E in human subjects. Br J Nutr 2000;84:261–7.
58. Tofler GH, Stec JJ, Stubbe I, et al. The effect of vitamin C supplementation on coagulability and lipid levels in healthy male subjects. Thromb Res 2000;100:35–41.
59. Martinez-Abundis E, Pascoe-Gonzalez S, Gonzalez-Ortiz M, Mora-Martinez JM, Cabrera-Pivaral CE. Effect of oral administration of ascorbic acid on insulin sensitivity and lipid profile in obese individuals. Rev Invest Clin 2001;53:505–10.
60. Shidfar F, Keshavarz A, Jallali M, Miri R, Eshraghian M. Comparison of the effects of simultaneous administration of vitamin C and omega-3 fatty acids on lipoproteins, apo A-I, apo B, and malondialdehyde in hyperlipidemic patients. Int J Vitam Nutr Res 2003;73:163–70.
61. McRae M, Richardson D. A comparative study on the efficacy of niacin, garlic, vitamin C, pantethine, chromium, gugulipid in reducing serum cholesterol and triglycerides: a review and statistical analysis of clinical trials from 1970 to 2001. J Am Coll Nutr 2002;21:490.
62. Rivers JM. Safety of high-level vitamin C ingestion. Int J Vitam Nutr Res Suppl 1989;30:95–102.
63. Jacob RA, Sotoudeh G. Vitamin C function and status in chronic disease. Nutr Clin Care 2002;5:66–74.
64. McKenney J. New perspectives on the use of niacin in the treatment of lipid disorders. Arch Intern Med 2004;164:697–705.
65. Stevinson C, Pittler MH, Ernst E. Garlic for treating hypercholesterolemia. A meta-analysis of randomized clinical trials. Ann Intern Med 2000;133:420–9.
66. Holloway DE, Rivers JM. Influence of chronic ascorbic acid deficiency and excessive ascorbic acid intake on bile acid metabolism and bile composition in the guinea pig. J Nutr 1981;111:412–24.
67. Duane WC, Hutton SW. Lack of effect of experimental ascorbic acid deficiency on bile acid metabolism, sterol balance, and biliary lipid composition in man. J Lipid Res 1983;24:1186–95.
68. Bates CJ, Mandal AR, Cole TJ. HDL cholesterol and vitamin-C status. Lancet 1977;2:611.
69. Aulinskas TH, Van der Westhuyzen DR, Coetzee GA. Ascorbate increases the number of low density lipoprotein receptors in cultured arterial smooth muscle cells. Atherosclerosis 1983;47:159–71.
70. Balkan J, Dogru-Abbasoglu S, Aykac-Toker G, Uysal M. Serum prooxidant-antioxidant balance and low-density lipoprotein oxidation in healthy subjects with different cholesterol levels. Clin Exp Med 2004;3:237–42.
71. Jialal I, Vega GL, Grundy SM. Physiologic levels of ascorbate inhibit the oxidative modification of low density lipoprotein. Atherosclerosis 1990;82:185–91.
72. Padayatty SJ, Katz A, Wang Y, et al. Vitamin C as an antioxidant: evaluation of its role in disease prevention. J Am Coll Nutr 2003;22: 18–35.
73. Jialal I, Fuller CJ. Effect of vitamin E, vitamin C and beta-carotene on LDL oxidation and atherosclerosis. Can J Cardiol 1995;11:97G-103G.
74. Anderson D, Phillips BJ, Yu TW, Edwards AJ, Ayesh R, Butterworth FR. The effects of vitamin C supplementation on biomarkers of oxygen radical generated damage in human volunteers with low or high cholesterol levels. Environ Mol Mutagen 1997;30:161–74.
75. Van Hoydonck PG, Schouten EG, Manuel-Y-Keenoy B, van Campenhout A, Hoppenbrouwers KP, Temme EH. Does vitamin C supplementation influence the levels of circulating oxidized LDL, sICAM-1, sVCAM-1 and vWF-antigen in healthy male smokers? Eur J Clin Nutr 2004;58:1587–93.
76. Leonhardt ET. Effect of vitamin E on serum cholesterol and triglycerides in hyperlipidemic patients treated with diet and clofibrate. Am J Clin Nutr 1978;31:100–5.
77. Bolster M, Duggan PF, Cole M, Crowley M. Lack of effect of ingestion of vitamin E on lipoprotein-cholesterol fractions in healthy adults. Ir Med J 1983;76:152–4.
78. Stampfer MJ, Willett W, Castelli WP, Taylor JO, Fine J, Hennekens CH. Effect of vitamin E on lipids. Am J Clin Pathol 1983;79:714–6.
79. DeMaio SJ, King SB 3rd, Lembo NJ, et al. Vitamin E supplementation, plasma lipids and incidence of restenosis after percutaneous transluminal coronary angioplasty (PTCA). J Am Coll Nutr 1992;11: 68–73.
80. Mensink RP, van Houwelingen AC, Kromhout D, Hornstra G. A vita-

min E concentrate rich in tocotrienols had no effect on serum lipids, lipoproteins, or platelet function in men with mildly elevated serum lipid concentrations. Am J Clin Nutr 1999;69:213–9.

81. Ribaya-Mercado JD, Ordovas JM, Russell RM. Effect of beta-carotene supplementation on the concentrations and distribution of carotenoids, vitamin E, vitamin A, and cholesterol in plasma lipoprotein and non-lipoprotein fractions in healthy older women. J Am Coll Nutr 1995;14:614–20.
82. Collins J, Arjmandi B, Claypool P, Perkins-Veazie P, Baker R, Clevidence B. Lycopene from two food sources does not affect antioxidant or cholesterol status of middle-aged adults. Nutr J 2004;3:15.
83. Kaikkonen J, Nyyssonen K, Porkkala-Sarataho E, et al. Effect of oral coenzyme Q10 supplementation on the oxidation resistance of human VLDL+LDL fraction: absorption and antioxidative properties of oil and granule-based preparations. Free Radic Biol Med 1997;22: 1195–202.
84. Xu Z, Hua N, Godber JS. Antioxidant activity of tocopherols, tocotrienols, and gamma-oryzanol components from rice bran against cholesterol oxidation accelerated by 2,2′-azobis(2-methylpropionamidine) dihydrochloride. J Agric Food Chem 2001;49: 2077–81.
85. Burr ML, Bates CJ, Goldberg G, Butland BK. Vitamin C and cholesterol in the elderly. Hum Nutr Clin Nutr 1985;39:387–8.
86. Levine M, Conry-Cantilena C, Wang Y, et al. Vitamin C pharmacokinetics in healthy volunteers: evidence for a recommended dietary allowance. Proc Natl Acad Sci USA 1996;93:3704–9.
87. Levine M, Wang Y, Padayatty SJ, Morrow J. A new recommended dietary allowance of vitamin C for healthy young women. Proc Natl Acad Sci 2001;98:9842–6.
88. Knekt P, Ritz J, Pereira MA, et al. Antioxidant vitamins and coronary heart disease risk: a pooled analysis of 9 cohorts. Am J Clin Nutr 2004;80:1508–20.
89. Gupta R, Singh AK, Basira R, Gupta N, Kanodia A, Gupta KD. Influence of total cholesterol levels on long-term mortality in coronary heart disease: a reappraisal. Indian Heart J 2000; 52(1): 23–8.