TOPICAL REVIEW

Chronic vitamin C deficiency increases the risk of cardiovascular diseases*

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Abstract

The studies on experimental animals (guinea pigs, monkeys, fish) have confirmed the important role of ascorbic acid deficiency in the development of hypercholesterolemia and atherosclerosis, but the clinical experience is not quite uniform. Metaanalyses of randomized controlled trials performed on subjects without established vitamin C-deficiency conclud that the evidence of the presence or absence of benefits derived from the ability of ascorbic acid to prevent cardiovascular diseases is not sufficient. This review is an outline of numerous clinical, epidemiological and prospective studies that have found a positive role of vitamin C in the prevention of atherosclerosis. If we admit the possibility that vitamin C deficiency is a significant risk factor of atherogenesis, due to ethical reasons it is impossible to perform long-term controlled trials on subjects with proved vitamin C deficiency, to recommend them not to change their nutrition and lifestyle, and to administer placebo to the control group. Therefore the proof of atherogenic effect of chronic vitamin C deficiency is limited to indirect evidence only. In this review many new data on the positive effects of ascorbic acid on human cardiovascular system are summarized and the mechanisms of its protective influence on blood vessels are discussed *(Fig.5, Ref. 45)*. Full Text (Free, PDF) *www.bmj.sk*.

Key words: vitamin C, atherosclerosis, hypercholesterolemia, lipoproteins LDL-HDL, epidemiology.

After experimental studies on vitamin C deficiency as a risk factor of atherosclerosis had been published in the second half of last century (1–4) and after Linus Pauling, double Nobel prize winner (5) had accepted these opinions, the interest in use of vitamin C in cardiovascular diseases prevention has spread significantly. Virtually, all of the studies on experimental animals have confirmed earlier findings, but the clinical experience is not quite uniform (6). The objective of this communication is to outline recent studies conducted mainly on various human populations and published after the year 1990.

Vitamin C and cardiovascular diseases in humans

Numerous data obtained on a large number of people show lower total and cardiovascular mortality in subjects well-supplied with vitamin C. A large international team has joined 9 main studies on the influence of food antioxidants on occurrence of cardiovascular diseases and deaths on a group of 293,172 people (!). They found out that the people who had consumed preparations containing vitamin C had the risk of a cardiovascular event lowered by 27 % (7). These data are in accordance with many other authors' data on positive influence of vitamin C in prevention of cardiovascular diseases (8–16).

American authors (17) who specified the levels of various vitamins in blood in 1214 people at the age of above 75 years and followed them for 4.4 years, found a close indirect relationship between the level of vitamins and mortality (total and cardiovascular) in the case of vitamin C only (Fig. 1). People with vitamin C deficiency had double mortality in comparison with people well-supplied with ascorbate. They conclude that the level of vitamin C in blood predicts mortality of elder people very well.

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* The author of this review was by B. Sardi (USA) declared as the world's leading vitamin C researcher. www.knowledgeofhealth.com.

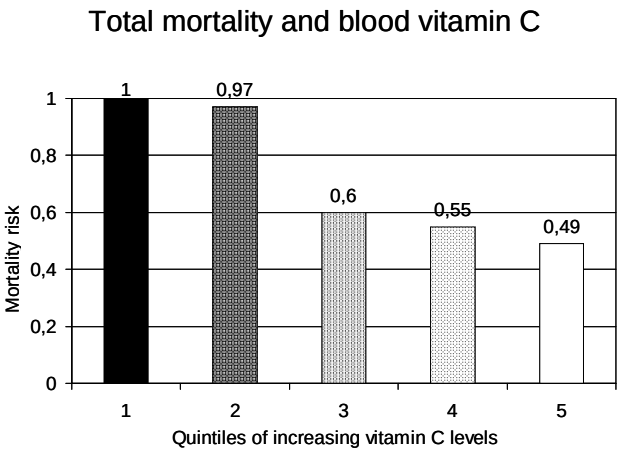

Fig. 1. Decrease in total mortality in old persons with increasing quintile of vitamin C blood concentration. According to Fletcher et al (17).

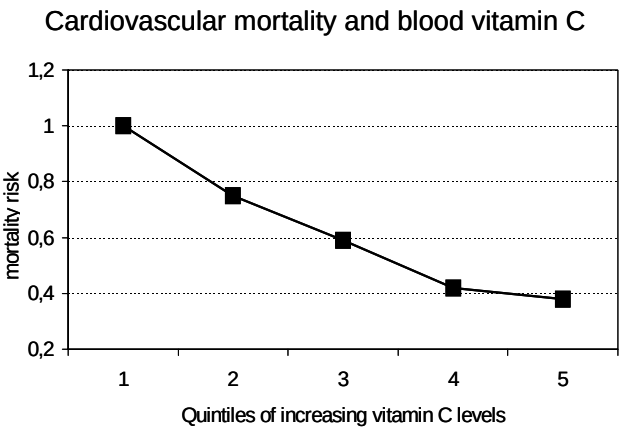

Fig. 2. Decrease in the relative risk of cardiovascular mortality with increasing quintile of vitamin C levels in the blood. According to Khaw et al (16).

In Great Britain the relationship between the level of ascorbic acid in plasma and cardiovascular mortality in 19,496 people at the age of 45–79 years in a prospective four-year study was followed (16). The risk of cardiovascular mortality was more than doubled in people with vitamin C deficiency in comparison with people well-supplied with ascorbic acid (Fig. 2). The relationship between mortality and the level of ascorbic acid in plasma was continuous. The increase in the ascorbate level by 20 μmol/l, which is equivalent to daily consumption of about 50 g of vegetables or fruit, caused a decrease in total mortality by 20 %. The authors conclude that a small increase in vegetable or fruit consumption is connected with increased prevention of cardiovascular diseases. In a Finnish prospective study conducted on 1605 men at the age of 42–60 years, their health condition was monitored for 5 years after the analysis of vitamin C content in plasma and composition of their diet (12). In people with vitamin C deficiency (the level in plasma below 11.4 μmol/l, i.e. 0.2 mg %)

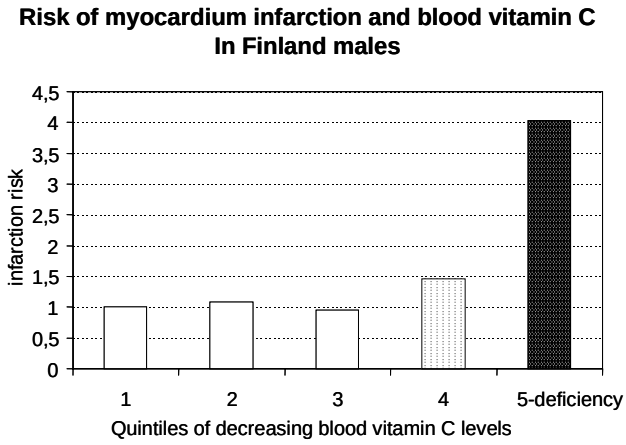

Fig. 3. Significant increase in the risk of myocardial infarction in men with biochemically proved vitamin C-deficiency. According to prospective study of Nyyssönen et al (12).

the risk of a heart attack was increased severely (Fig. 3). After the correction according to age and smoking this number got lower but it was still significantly higher than in all of the other groups better supplied with vitamin C.

The protective effect of vitamin C or fruit on cardiovascular system has been described as well in a number of other English (18), American (19), Finnish (20), Chinese (21), Japanese (22) and Austrian (23) reports. Entering the query "vitamin C – cardiovascular disease" in the GOOGLE gave 834 responses. The well-known protective effect of the Mediterranean diet is also put down to the high content of vitamin C besides the high content of mono-unsaturated fatty acids and low content of saturated fats (24).

The results of studies on the protective effect of vitamin C in smokers published quite recently are interesting. Smoking is a well known risk factor of atherogenesis. South-Korean authors (25) found out that high intake of vitamin C was connected with a lower risk of non-fatal heart attacks in strong smokers. Vascular endothelial growth factor (VEGF) plays an important role in atherogenesis. This factor stimulates monocyte migration, but not in smokers. Administration of vitamin C normalized the monocyte reaction (26). Administration of vitamin C lowered the oxidation stress when caused by smoking (27). These findings are important because the occurrence of vitamin C deficiency in smokers has been known for a long time.

It is necessary to stress out that there are also some studies that report a slight or non-significant effect of vitamin C on plasmatic lipids or atherogenesis in humans (28–30).

Mechanism of protective activity of vitamin C

1. Effect on cholesterol metabolism

Besides smoking, hypercholesterolemia is an important risk factor of cardiovascular diseases. Chronic vitamin C deficiency lowers cholesterol transformation into its main catabolic product -cholic acids due to lowered activity of the key enzyme of

cholesterol catabolism - 7-alpha-cholesterol hydroxylase (3, 4). Vitamin C inhibits the key enzyme of endogenous cholesterol synthesis in human leukocytes (31). Therefore it is understandable that in case of vitamin C deficiency cholesterol accumulates in the body, and vice versa, after administration of ascorbic acid the cholesterol concentration decreases. Ascorbate deficiency manifests not only by the increase in the cholesterol level in blood, its accumulation in arteries (4), but also by increased formation of cholesterol bile stones in humans (32).

2. Lowering of blood pressure

It is well-known that besides smoking and hypercholesterolemia, hypertension is another serious risk factor of atherogenesis. In five studies it has been found out that people well-supplied with vitamin C are less endangered by hypertension than those with deficient supply with ascorbic acid. Some other authors did not observe such an effect.

3. Antioxidant effects of ascorbic acid

It has been known for a long time that the oxidized form of the main cholesterol carrier in plasma – LDL (low-density lipoproteins) is more dangerous in respect of atheroma development than intact LDL. Owing to its strong antioxidant effects, the ascorbic acid protects LDL from peroxidation, and it keeps LDL ability to bind to LDL-receptors (34–36). Orange juice has the same effect as the ascorbic acid (37). Owing to its antioxidant effects, carotid atherosclerosis is less pronounced in men with high blood levels of vitamins C and E (38). By means of the same mechanism, ascorbic acid has a protective effect also in the development of Alzheimer disease (39).

4. Effect of vitamin C on haemostatic factors

In cardiovascular disease the development of thrombosis plays an important role. It has been found out that deficiency in vitamin C increases the blood coagulation, and that administration of ascorbic acid normalizes the situation (40, 41). Vitamin C has a beneficial effect on endothelial function in children with familial hyperlipemia.

Male premature cardiovascular mortality (0-64 years) in EU, Slovakia and Czech Republic

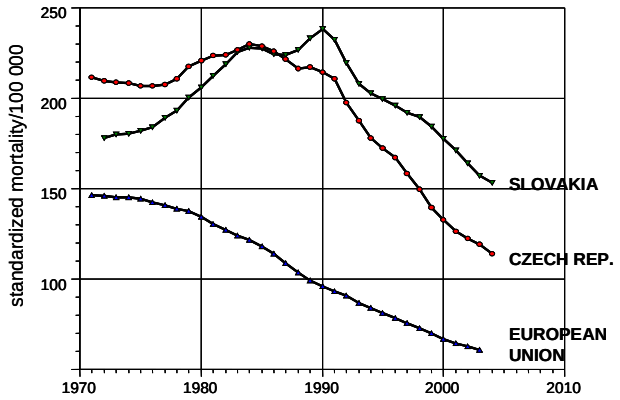

Fig. 4. Decrease in the standardized premature male cardiovascular mortality (age 0–64 years) in the European Union, Slovak and Czech Republics. According to WHO (42).

Male premature cardiovascular mortality (0-64 years) in Russia, Belorus and Ukraine

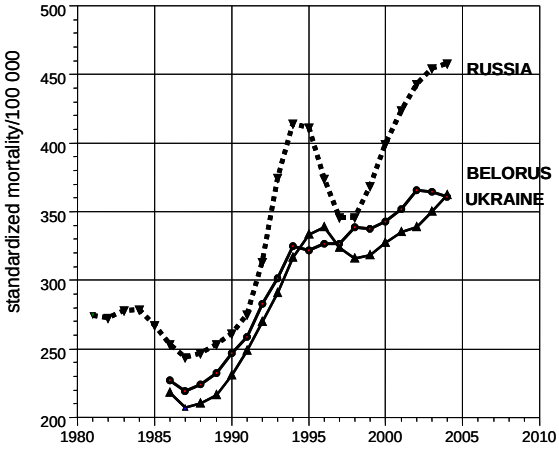

Fig. 5. Increase in the standardized premature male cardiovascular mortality (age 0–64 years) in the European countries formed in the territory of the former USSR. According to WHO (42).

Vitamin C deficiency and epidemiology of cardiovascular mortality

The extremely high cardiovascular mortality in Western Europe, especially in Finland in the 1960's led to a series of remedial measures, which were especially the substitution of butter for vegetable fats, better monitoring and therapy of hypertension, decrease in smoking and increase in vegetable and fruit consumption. Under the thumb of studies about the protective effects of vitamin C, the consumption of natural and synthetic ascorbic acids has increased. In the whole of Western Europe, and especially in Finland and European Union, premature cardiovascular mortality fell rapidly; this phenomenon moved also to Central Europe after the fall of totalitarian regimes and resulted in an increase in fruit, juices and vegetable consumption (42) (Fig. 4). It is possible that the decrease in chronic vitamin C deficiency saved millions of lives in Europe. On the other hand, the cardiovascular mortality is still growing in the countries established in the territory of the former USSR (42) (Fig. 5). It is well-known that in this area chronic vitamin C deficiency persists especially in long winter periods and that it may cause, along with other risk factors (e.g. alcoholism, smoking and psychological factors) extremely high cardiovascular mortality.

Conclusion

The sceptical views on the usefulness of vitamin C in the prevention of cardiovascular diseases object that even in the face of many positive reports the evidence of vitamin C deficiency is

not direct (43–45). These authors assert that the final proof could be given by double-blinded study in which vitamin C or placebo would be administered to people with vitamin C deficiency, and in which the effect (total and cardiovascular mortality, non-fatal cardiovascular events, HDL and LDL lipoproteins levels, blood pressure etc.) would be followed for at least 5 years. As an exemplar they mention perfect studies conducted with statins (4S, WOSCOP and CARE). Disregarding the fact that these are financially extremely demanding projects, such a project would be infeasible for working and ethical reasons. It would be necessary to select biochemically at least 5,000 people by analyzing their levels of ascorbic acid in blood. Such a selection could be carried out in Russia, but hardly in the European Union or USA. If we admit the probable possibility that vitamin C deficiency is a significant risk factor of atherogenesis, it is not possible to leave these people with a biochemically proved vitamin C deficiency for 5 years, to recommend them not to change their diet and to administer them placebo. Therefore the proof of atherogenic effect of chronic vitamin C deficiency is limited to indirect evidence only.

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