Nutritional Supplement Program Halts Progression of Early Coronary Atherosclerosis Documented by Ultrafast Computed Tomography

Aleksandra Niedzwiecki Ph.D. and **Matthias Rath M.D.**

Introduction

According to the World-Health Organization, over 12 million people die every year from heart attacks, strokes and other forms of cardiovascular disease.[1] Current concepts of the pathogenesis of cardiovascular disease focus on elevated plasma risk factors damaging the vascular wall and thereby initiating atherogenesis and cardiovascular disease.[2-4] Accordingly, drugs lowering cholesterol and modulating other plasma risk factors have become a predominant therapeutic approach in the prevention of cardiovascular disease.

A new scientific rationale about the initiation of atherosclerosis and cardiovascular disease was proposed by one of us[5,6]. It can be summarized as follows: cardiovascular disease is primarily caused by chronic deficiencies of vitamins and other essential nutrients with defined biochemical properties, such as coenzymes, cellular energy carriers, and antioxidants.[7,8] Chronic depletion of these essential nutrients in endothelial and vascular smooth muscle cells impairs their physiological function. For example, chronic ascorbate deficiency, similar to early scurvy, leads to morphological impairment of the vascular wall and endothelial microlesions, histological hallmarks of early atherosclerosis. [9-11] Consequently, atherosclerotic plaques develop as the result of an overcompensating repair mechanism comprising deposition of systemic plasma factors as well local cellular responses in the vascular wall.[5,6] This repair mechanism is primarily exacerbated at sites of hemodynamic stress, explaining the predominantly local development of atherosclerotic plaques in coronary arteries and myocardial infarction as the most frequent clinical manifestation of cardiovascular disease.

Animal studies have confirmed this scientific rationale for the combination of ascorbate with other essential nutrients in the prevention and treatment of cardiovascular disease.[12]

Subjects and Methods

Patients

A total of 55 patients, 50 men and 5 women, with documented coronary artery disease assessed by Ultrafast CT, were recruited for the study. The inclusion criterion was the availability of a high quality Ultrafast CT scan from a previous visit to the Heart Scan facility in South San Francisco. At the beginning of the study each patient completed a comprehensive questionnaire, which was updated after six months and after 12 months. This questionnaire included medical history, previous cardiac events, and cardiovascular risk factors, as well as individual life style data. Specific questions related to the patientsÕ regular diet, such as strictly vegetarian diet, predominantly fruits and vegetables, predominantly meat, fish or poultry; the daily intake of different vitamins and other essential nutrients; and the frequency of physical exercise by the patient. The laboratory tests available documented a heterogeneous population with respect to plasma cholesterol and triglycerides. About half of the patients were taking different types of prescription medication, including calcium antagonists, nitrates, betablockers, and cholesterol-lowering drugs. Before entering the study, the patients were instructed not to change their diet or lifestyle other than adding the nutritional

supplement program tested. Any changes were to be documented in their questionnaires. Compliance with the nutritional supplement program was monitored in the questionnaires, through telephone calls and during the control visits.

Composition and Administration of Nutritional Supplement Program

The following daily dosages of nutritional supplements were taken for a period of one year: Vitamins: Vitamin C 2700 mg, Vitamin E(d-Alpha-Tocopherol) 600 IU, Vitamin A (as Beta-Carotene) 7,500 IU, Vitamin B-1 (Thiamine) 30 mg, Vitamin B-2 (Riboflavin) 30 mg, Vitamin B-3 (as Niacin and Niacinamide) 195 mg, Vitamin B-5 (Pantothenate) 180 mg, Vitamin B-6 (Pyridoxine) 45 mg, Vitamin B-12 (Cyanocobalamin) 90 mcg, Vitamin D (Cholecalciferol) 600 IU. Minerals: Calcium 150 mg, Magnesium 180 mg, Potassium 90 mg, Phosphate 60 mg, Zinc 30 mg, Manganese 6 mg, Copper 1500 mcg, Selenium 90 mcg, Chromium 45 mcg, Molybdenum 18 mcg. Amino acids: L-Proline 450 mg, L-Lysine 450 mg, L-Carnitine 150 mg, L-Arginine 150 mg, L-Cysteine 150 mg. Coenzymes and other nutrients: Folic Acid 390 mcg, Biotin 300 mcg, Inositol 150 mg, Coenzyme Q-10 30 mg, Pycnogenol 30 mg, and Citrus Bioflavonoids 450 mg.

Monitoring of Coronary Artery Disease

The extent of coronary calcification was measured non-invasively with an Imatron C-100 Ultrafast CT scanner in the high-resolution volume mode, using a 100- millisecond exposure time. ECG triggering was used so that each image was obtained at the same point in the diastole, corresponding to 80% of the RR interval. In each scan, 30 consecutive images were obtained at 3-mm intervals beginning 1 cm below the carina and progressing caudally to include the entire length of the coronary arteries. The scans at study entry and after 6 and 12 months of the study included a second scan sequence of 30 images at 3 mm intervals across the entire heart. The 30 images of the second scan were taken between the 3 mm intervals of the first scan resulting in a scanning of the heart at an interval of 1.5 mm. Total radiation exposure using this technique was <1rad per patient (<.01Gy).

The scan threshold was set at 130 Hounsfield units (Hu) for identification of calcified lesions. The minimum area to differentiate calcified lesions from CT artifact was 0.68 mm2. The lesion score, also designated Coronary Artery Scanning (CAS) score, was calculated by multiplying the lesion area by a density factor derived from the maximal Hounsfield unit within this area.[13] The density factor was assigned in the following way: 1 for lesions with a maximal density with 130-199 Hu, 2 for lesions with 200-299 Hu, 3 for lesions with 300-399 Hu and 4 for lesions > 400 Hu. The total calcium areas and CAS scores of each Ultrafast CT scan were determined by summing individual lesion areas or scores from the left main, left anterior descending, circumflex, and right coronary artery.

Several studies have confirmed an excellent correlation of the extent of coronary artery disease as assessed by Ultrafast CT scanning when compared to angiographic and histomorphometric methods.[13-15] Considering the accuracy and the non-invasive approach, Ultrafast CT was the method of choice for an intervention study that included early, asymptomatic stages of coronary artery disease.
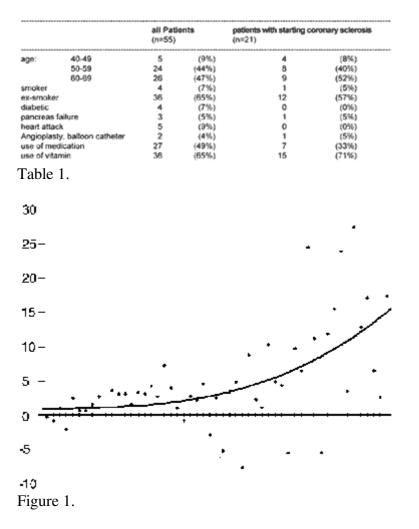
Statistical Analysis

The growth rate of coronary calcifications was calculated as the quotient of the differences in the calcification areas or CAS scores between two scans divided by the months between these scans according to the formula (Area2-Area1):(Date2-Date1), or (CAS score2-CAS score1):(Date2-Date1) respectively. The data were analyzed using standard formulas for means, medians, and standard error of the means (SEM). PearsonÕs correlation coefficient was used to determine the association between continuous variables. One tailed Student t-test was used to analyze differences between mean values, with a significance defined at <0.5. Progression of calcification was predicted by linear extrapolation.

The distribution of the growth rate of CAS scores was described by a smooth curve resulting from a third order polynominal fit (y=a + bx3, where a = 0.9352959, b = 8.8235 x 10-5).

Results

The aim of this study was to determine the effect of a defined nutritional supplement program on the natural progression of coronary artery calcification particularly in its initial stages as measured by Ultrafast CT. We therefore evaluated the results of the entire study group (n=55) and of a subgroup of 21 patients with early coronary artery calcification, as defined by a CAS score of <100.

Table 2 separately lists the characteristics of the study population assessed by the questionnaire for all patients and for a subgroup with early coronary artery disease.

		all Patients (n=55)		patients with starting coronary sclerosis (n=21)	
age:	40-49	5	(9%)	4	(8%)
	50-59	24	(44%)	8	(40%)
	60-69	26	(47%)	9	(52%)
smoker		4	(7%)	1	(5%)
ex-smoker		36	(65%)	12	(57%)
diabetic		4	(7%)	0	(0%)
pancreas failure		3	(5%)	1	(5%)
heart attack		5	(9%)	0	(0%)
Angioplasty, balloon catheter		2	(4%)	1	(5%)
use of medication		27	(49%)	7	(33%)
use of vitamin		36	(65%)	15	(71%)

Table 1.

Figure 1.

This is the first intervention study using Imatron's Ultrafast CT technology. One of the first aims of this study was to determine the rate of natural progression of coronary calcium deposits in situ , without the intervention of the nutritional supplement program. Figure 1 shows the distribution of the monthly progression of calcifications in the coronary arteries of all 55 patients in relation to their CAS score at study entry.

We found that the higher the CAS score was initially, without intervention, the faster the coronary calcification progressed. Accordingly, the average monthly growth rate of coronary calcifications ranged from 1 CAS score per month in patients with early coronary heart disease to more than 15 CAS score per month in patients with advanced stages of coronary calcifications. The growth pattern of coronary calcifications can be described as a third order polynomial fit curve. The exponential

shape of this curve signifies a first quantification of the aggressive nature of coronary atherosclerosis and emphasizes the importance of early intervention.

The changes in the natural progression rate of coronary artery calcification before the nutritional supplement program (-NS) and after one year on this program (+NS) are shown in Figure 2. The results are presented separately for the calcified area and the CAS score.

As presented in Figure 2.a. the average monthly growth of calcified areas for all 55 patients decreased from 1.24 mm2/month (SEM +/- 0.3) before the nutritional supplement program (-NS) to 1.05 mm2/month (+/- 0.2) after one year on this program (+NS).For patients with early coronary artery disease (Figure 2b), the average monthly growth of the calcified area decreased from 0.49 mm2/month (+/- 0.16) before taking the nutritional supplements (-NS) to 0.28 mm2/month (+/- 0.09) after one year on this program (+NS).
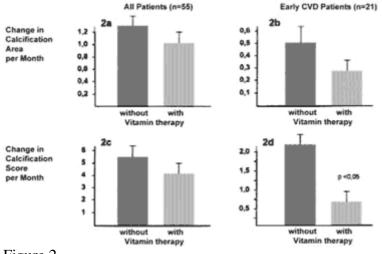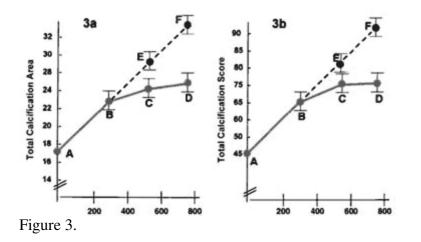

Figure 2.

As shown in Figure 2.c the average monthly changes in the total CAS score (calcified area X density of calcium deposits) for all 55 patients had decreased after one year on the nutritional supplement program by 11%, from 4.8 CAS score/month (SEM +/-0.97) before the program (-NS) to 4.27 CAS score /month(+/- 0.87) (+NS). In patients with early coronary artery disease (Figure 2.d) the average monthly growth of the total CAS score decreased during the same time by as much as 65%, from 1.85 CAS score /month (+/-0.49) before the nutritional supplement program (-NS) to 0.65 CAS score /month (+/- 0.36) on this program (+NS). The slow-down of the progression of coronary calcification during this nutritional supplement intervention for CAS scores of patients with early coronary artery disease was statistically significant ($p<0.05$)(Figure 2.d). For the other three sets of data the decrease of coronary calcifications with the nutritional supplement program was evident; however, largely due to the wide range of calcification values at study entry reflecting the different stages of coronary artery disease, it did not reach statistical significance.

It is noteworthy that the decrease in the CAS scores during intervention with nutritional supplements were more pronounced than for the calcified areas. This indicates a decrease in the density of calcium in addition to a reduction in the area of coronary calcium deposits during nutritional supplement intervention.

Ultrafast CT scans at the beginning of the study and after 12 months on the nutritional supplement program, were complemented by a control scan after 6 month, allowing for additional insight into the time required for the nutritional supplements to exert their therapeutic effect. This additional evaluation was particularly important for early forms of coronary artery disease, because any therapeutic approach that can halt progression of early coronary calcification would ultimately prevent myocardial infarctions.

Figure 3 shows the average coronary calcification areas (Figure 3.a) and total CAS scores (Figure 3.b) for patients with early coronary artery disease measured during different scanning dates before and during the course of the study. The actual coronary calcification values for areas and total CAS scores during nutritional supplement intervention are compared to the predicted values obtained from linear extrapolation of the growth rate without intervention. The letters A to D mark the different time points at which Ultrafast CT scans were performed. AB represents the changes in coronary calcification before intervention with nutritional supplement for the areas (Figure 3.a) and CAS scores (Figure 3.b). Accordingly, BC represents calcification changes during the first six months on the nutritional supplement program and CD changes during the second six months on the program. The calculated progression rate for coronary calcifications without therapeutic intervention by the nutritional supplement program is marked by a dotted line (B through F).

As seen in Figure 3.a without the nutritional supplement program, the average area of coronary calcifications in patients with early coronary artery disease increased from 17.62 mm2 (+/- 1.0) at time point A to 23.05 mm2 (+/- 1.8) at time point B. Thus, the annual extension of calcified areas without intervention was assessed with 31 %. At this progression rate, the average calcified area would reach 26.3 mm2 after six months (point E) and 29.8 mm2 after twelve months (point F). The nutritional supplement intervention, resulted in an average calcified area of 25.2 mm2 (+/-2.2) after six months and of 27.0 mm2 (+/-1.7) after 12 months, reflecting a 10% decrease compared to the predicted value.

Figure 3.

Analogous observations were made for the total CAS before and during the nutritional supplement program. Figure 3.b shows that the CAS score before the nutritional supplement program increased by 44% per year, from 45.8 (+/- 3.2) (point A) to 65.9 mm2 (+/- 5.2) (point B). At this progression rate the total CAS score, without the nutritional supplement program, would reach an average of 77.9 after six months (point E) and of 91 (point F) after twelve months. In contrast to this trend the actual CAS score values measured with the nutritional supplement program were 75.8 (+/-6.2) after 6 months (point C) and 78.1 (+/-5.1) after 12 months (point D). Thus, the progression of coronary calcification as determined by the total CAS scores decreased significantly during the second six months of nutritional supplement intervention (CD). The total score after twelve months on the nutritional supplement program was only 3% higher than after six months (CD), as compared to the projected increase of 17% (EF), indicating that during the second six months on the nutritional supplement program the process of coronary calcification has practically stopped.

Figure 4 shows the actual Ultrafast CT scans of a 51 year old patient with early, asymptomatic, coronary artery disease. The patientsÕ first Ultrafast CT scan was performed in 1993 as part of an annual routine check-up. The scan film revealed small calcifications in the left anterior descendent coronary artery as well as in the right coronary artery. The second CT scan was performed one year later at which time the initial calcium deposits had further increased. Figure 4.a shows two Ultrafast CT scan images taken before the nutritional supplement program. Subsequently, the patient started on

the nutritional supplement program. About one year later the patient received a control scan. At this time point, coronary calcifications were not found (Figure 4b), indicating the natural reversal of coronary artery disease.
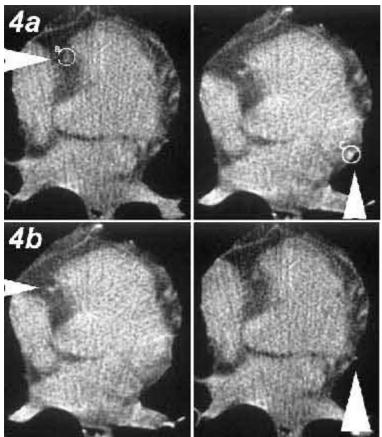

Figure 4.

Discussion

This is the first study that provides quantifiable data from in situ measurements about the natural progression rate of coronary artery disease. Although atherosclerotic plaques have a complex histomorphological composition, calcium dispersion within these plaques has been shown to be an excellent marker for their advancement.[11,13] Our study determined that the calcified vascular areas expand at a rate between 5 mm2 (early atherosclerotic lesions) and 40 mm2 (advanced atherosclerotic lesions). Before the nutritional supplement program the average annual increase of total coronary calcification was 44% (Figure 1). Considering the exponential increase of coronary calcification, it is evident that the control of cardiovascular disease has to focus on early diagnosis and early intervention.

Today, the diagnostic assessment of individual cardiovascular risk is largely confined to the measurement of plasma cholesterol and other risk factors with little correlation to the extent of atherosclerotic plaques. More accurate methods, such as coronary angiography, are confined to advanced, symptomatic, stages of coronary artery disease. Ultrafast CT provides the diagnostic option to quantify coronary artery disease non-invasively in its early stages.[14,15]

The most important finding of this study is that coronary artery disease can be effectively prevented and treated by natural means. This nutritional supplement program was able to decrease the progression of coronary artery disease within the relatively short time of one year, irrespective of the stage of this disease. Most significantly, in patients with early coronary calcifications this nutritional

supplement program was able to essentially stop its further progression. In individual cases with small calcified deposits, nutritional supplement intervention led to their complete disappearance (Figure 4).

We postulate that the nutritional supplement program tested in this study initiates the reconstitution of the vascular wall. Restructuring of the vascular matrix is facilitated by several nutrients tested, such as ascorbate (vitamin C), pyridoxine (vitamin B-6), L-lysine, and L-proline, as well as the trace element copper. Ascorbate is essential for the synthesis and hydroxylation of collagen and other matrix components,[16-18] and can be directly and indirectly involved in a variety of regulatory mechanisms in the vascular wall from cell differentiation to distribution of growth factors.[19,20] Pyridoxine and copper are essential for the proper cross-linking of matrix components.[8] L-lysine and L-proline are important substrates for the biosynthesis of matrix proteins; they also competitively inhibit the binding of lipoprotein(a) to the vascular matrix, facilitating the release of lipoprotein(a) and other lipoproteins from the vascular wall.[5,12,21] Ascorbate and -tocopherol have been shown to inhibit the proliferation of vascular smooth muscle cells.[22-24] Moreover, tocopherols, beta-carotene, ascorbate, selenium and other antioxidants scavenge free radicals and protect plasma constituents, as well as vascular tissue, from oxidative damage.[25,26] In addition, nicotinate, riboflavin, pantothenate, carnitine, coenzyme Q-10, as well as many minerals and trace elements, function as cellular cofactors in form of NADH, NADPH, FADH, Coenzyme A and other cellular energy carriers.[8] The results of this study confirm that maintaining the integrity and physiological function of the vascular wall is the key therapeutic target in controlling cardiovascular disease. This also corroborates early angiographic findings that supplemental vitamin C may halt the progression of atherosclerosis in femoral arteries.[27]

These conclusions are even more relevant since deficiencies of essential nutrients are common.[28,29] Moreover, many epidemiological and clinical studies have already documented the benefits of individual nutrients in the prevention of cardiovascular disease.[30-35] Compared to the high dosages of vitamins used in some of these studies the amounts of nutrients used in this study are moderate, indicating the synergistic effect of this program.

In this context, it seems appropriate to critically review some of the approaches currently used in the primary and secondary prevention of cardiovascular disease, including the extensive use of cholesterol-lowering drugs. An intervention study including lovastatin was performed with a highly selected group of hyperlipidemic patients, representing only an extremely narrow fraction of a normal population.[36] More recently, the reduction of myocardial infarctions and other cardiac events in patients taking simvastatin, led to recommendations for its long-term use even by normolipidemic patients.[37] However, because of their potential side-effects, the recommended use of these drugs has now been restricted to patients at high short term risk for coronary heart disease.[38]

Similarly, certain natural approaches to prevention of cardiovascular disease deserve a critical review. A program of rigorous diet and exercise program claims to be able to reverse coronary heart disease.[39] However, the published study does not provide compelling evidence documenting the regression of coronary atherosclerosis. Thus, the improved myocardial perfusion shown in that study, was likely the result of the physical training program, leading to an increased ventricular ejection fraction and an increased coronary perfusion pressure.

Considering the urgent need for effective and safe public health measures towards the control of cardiovascular disease, the validity of this study is of particular importance. In light of this, the following study elements are noteworthy.

1 The patients in this study served as their own controls before and during nutritional supplement intervention, thereby minimizing undesired co-variables such as age, gender, genetic predisposition, diet or medication.

2 Ultrafast CT has been extensively validated to assess the degree of coronary atherosclerosis, and it allowed quantification of coronary atherosclerotic plaques in situ.13-15 This diagnostic technique also minimizes errors as they occur in angiography studies in which vasospasms, formation or lysis of thrombi, and other events cannot be differentiated from progression or regression of atherosclerotic plaques. Moreover, Ultrafast CT provides valuable information about the morphological changes during progression and regression of atherosclerotic plaques, by quantifying not only the area of coronary calcifications but also their density. Furthermore, the automatic CT measurements of coronary calcifications eliminates human error in the evaluation of the data.

In summary, the results of this study imply that coronary heart disease is a preventable and essentially reversible condition. This study documents that coronary artery disease could be halted in its early stages by following this nutritional supplement program. These results were achieved within one year, suggesting that additional therapeutic benefits in patients with advanced coronary artery disease can be obtained by an extended use of this program. The continuation of this study is currently under way to document these effects. This nutritional supplement program signifies an effective and safe approach for the prevention and adjunct therapy of cardiovascular disease.

Acknowledgements

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