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Inverse correlation between the plasma level of antioxidant vitamins and the incidence of ischemic heart disease (IHD) in cross-sectional epidemiology

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Introduction

IHD is predicted by hitherto established risk factors such as hypercholesterolemia only to about 50%. Among candidates as complementary factors are aggressive oxygen species and thus also the radical scavengers, i.e. the antioxidants. In the acute reperfusion experiment hypoxia with subsequent reoxygenation results in a sudden burst of oxygen radicals which will seriously damage blood vessels as soon as the physiological radical scavengers such as the vitamins C, E and glutathion are exhausted. Exogenous peroxidized polyunsaturated fatty acids (PUFA) damage endothelial and heart muscle cells and provoke proliferation of smooth muscle cells, and cause even sudden death in animals. This can be prevented by vitamins C or E. Chronic marginal deficiency of vitamin C or E causes arteriosclerosis-like lesions in rodents and piglets. Experimental scurvy in man can suddenly cause cardiomegaly, electrocardiographic abnormalities and acute cardiac emergency. Arteriographically established IHD was reported to be inversely related to the status of vitamin C. Previous epidemiological evidence suggests that the vegetarian type of diet is associated with a lower mortality from IHD. Correspondingly, the standardized mortality for IHD in England, Wales, Scotland, Norway, and Israel seems to be inversely correlated to the calculated ascorbic acid intake from fresh fruits and green vegetables [lit. cit. 1]. In consequence, the actual plasma status of antioxidant vitamins remains to be evaluated with regard to IHD in westernized countries.

Results and discussion

The plasma level of ascorbic acid, α-tocopherol, β-carotene, retinol and selenium was measured in a standard period (January through April) in 6 pilot cohorts, each of about 100 males aged 40–49 years, from areas typical for either a very high incidence of IHD (North Karelia/Finland, Southwest Finland and Edinburgh/Scotland, with age-specific mortality rates of 481, 359 and 354/100000 males, 40–59 years of age), a medium incidence (Belfast/Northern Ireland, with 246 deaths from IHD/100000 males) and a fairly low incidence of IHD (Thun/semialpine Switzerland and Sapri/Southern Italy, with 105 and 107/100000 males). Since the median of total cholesterol is only relatively low in Italy (5.2 mM) and relatively high in North Karelia (6.4 mM) but very similar in all other areas (5.8–5.9 mM) the present study populations are particularly suited to search for risk factors other than cholesterol.
The medians of two essential plasma antioxidants varied inversely with the IHD mortality as follows [1, 2, 3]:

[1] Reporting for the International Collaborative Study on the Fatty-Acid-Antioxidant Hypothesis of Arteriosclerosis and the succeeding Optional Antioxidant Vitamin Study of the WHO/MONICA Project.

IHD mortality	low <130/100000	medium	high >300/100000	Δ
Vitamin C	≧35 μ*M*		20–31 μ*M*	−33% ($p<0.01$)
Cholesterol-standardized vitamin E	≧25 μ*M*		20–21.5 μ*M*	−25% ($p<0.01$)

The lowest vitamin C medians are near the borderline of accepted marginal vitamin C deficiency, the low values of lipid-standardized vitamin E (per 5.7 m*M* plasma cholesterol) are about twice the level associated with overt vitamin E deficiency (with severe neuromuscular disorders). These data actually confirm previous reports on at least seasonally critical vitamin C levels in Finland and the British Isles as well as a poor vitamin E status in Finland and Britain. The inverse correlation between the vitamin E status and IHD might have been overseen since in previous papers the vitamin E value was not lipid-standardized.

The Pearson's correlation coefficient for medians and IHD mortality were −0.53 for vitamin C ($p=0.28$), −0.89 for standardized vitamin E ($p=-0.019$), + 0.76 for total cholesterol ($p=0.08$) and with + 0.97 highest for total cholesterol/standardized vitamin E ($p=0.001$). By negating other risk factors of IHD, e.g. hypertension, a very tentative, exploratory mortality estimate for 3 independent variables follows the formula $759 + 978 \times$ median cholesterol $- 19 \times$ median vitamin C $- 679 \times$ median standardized vitamin E ($r=0.96$). The present data suggest at least that previously established risk factors of IHD, e.g. cholesterolemia, can be substantially complemented by the major dietary antioxidants, i.e. vitamin C and mainly standardized vitamin E [1, 2, 3].

Since the levels of vitamin A, β-carotene and selenium did not differ regularly they may only be of minor importance.

Pilot studies on PUFA of adipose tissue in high IHD areas (Finland and Scotland) versus a low IHD area (Italy) revealed also an inverse correlation of linoleic acid and the P/S ratio respectively with IHD [4]. Since linoleic acid-rich vegetable oils are a major albeit variable dietary source of vitamin E further studies are needed to evaluate the relative biological significance for IHD of PUFA and vitamin E and their optimal ratio for a presumable synergism respectively. Thus, for further cross-sectional studies the measurement of α-tocopherol and PUFA in membrane phospholipids has been included.

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