Papers

Antioxidant state and mortality from coronary heart disease in Lithuanian and Swedish men: concomitant cross sectional study of men aged 50

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Abstract

Objective: To investigate possible risk factors and mechanisms behind the four times higher and diverging mortality from coronary heart disease in Lithuanian compared with Swedish middle aged men.
Design: Concomitant cross sectional comparison of randomly selected 50 year old men without serious acute or chronic disease. Methods and equipment were identical or highly standardised between the centres.
Setting: Linköping (Sweden) and Vilnius (Lithuania).
Subjects: 101 and 109 men aged 50 in Linköping and Vilnius respectively.
Main outcome measures: Anthropometric data, blood pressure, smoking, plasma lipid and lipoprotein concentrations, susceptibility of low density lipoprotein to oxidation, and plasma concentrations of fat soluble antioxidant vitamins.
Results: Systolic blood pressure was higher (141 *v* 133 mm Hg, $P < 0.01$), smoking habits were similar, and plasma total cholesterol (5.10 *v* 5.49 mmol/l, $P < 0.01$) and low density lipoprotein cholesterol (3.30 *v* 3.68 mmol/l, $P < 0.01$) lower in men from Vilnius compared with those from Linköping. Triglyceride, high density lipoprotein cholesterol, and Lp(a) lipoprotein concentrations did not differ between the two groups. The resistance of low density lipoprotein to oxidation was lower in the men from Vilnius; lag phase was 67.6 *v* 79.5 minutes ($P < 0.001$). Also lower in the men from Vilnius were mean plasma concentrations of lipid soluble antioxidant vitamins (β carotene 377 *v* 510 nmol/l, $P < 0.01$; lycopene 327 *v* 615 nmol/l, $P < 0.001$; and lipid adjusted γ tocopherol 0.25 *v* 0.46 µmol/mmol, $P < 0.001$. α Tocopherol concentration did not differ). Regression analysis showed that the lag phase was still significantly shorter by 10 minutes in men from Vilnius when the influence of other known factors was taken into account.
Conclusions: The high mortality from coronary heart disease in Lithuania is not caused by traditional risk factors alone. Mechanisms related to antioxidant state may be important.

Introduction

Mortality from coronary heart disease has increased dramatically during the past 10-15 years in eastern Europe, especially in middle aged men, but it has decreased in western Europe.[1-3] Bobak and Marmot recently highlighted these diverging trends in mortality and the urgent need to investigate it.[4] Figure 1 shows an example of these trends in middle aged men in Lithuania and Sweden. The generally held view is that traditional risk factors for coronary heart disease—that is, high blood pressure, smoking, and dyslipidaemia—have the same predictive strength in eastern and western Europe and could explain these differences in mortality.[5] However, other factors may also be important. Studies have shown associations between the susceptibility of low density lipoprotein to oxidation and the severity of atherosclerosis.[6-9] Furthermore, antioxidant vitamins may have a protective role in coronary heart disease.[10] We compared men aged 50 in Linköping (Sweden) and Vilnius (Lithuania) to elucidate possible causes of the increased rate of coronary heart disease in Lithuania. We investigated traditional risk factors and other suggested mechanisms behind coronary heart disease such as the susceptibility of low density lipoprotein to oxidation and plasma concentrations of antioxidant vitamins.

Subjects and methods

The Linköping-Vilnius coronary disease risk assessment study was a cross sectional study conducted concomitantly in Vilnius (600 000 inhabitants) and Linköping (130 000 inhabitants) from October 1993 to June 1994. It was approved by the ethics committee of Linköping University. A list of randomly selected men born between 1 July 1943 and 30 June 1944 was obtained from the census register in each city. The exclusion criterion was having serious acute or chronic diseases because such diseases could influence the results of investigations or make participation impossible.

The experimental protocol was thoroughly standardised between the two centres. Biochemical analyses were performed in one laboratory, at Linköping, except for vitamin concentrations, which were meas-

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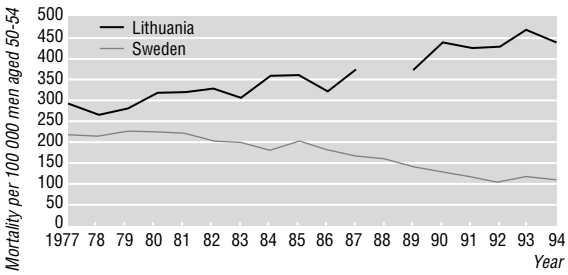

Fig 1 Mortality from coronary heart disease (International Classification of Diseases, codes 410-414) per 100 000 among 50-54 year old men in Lithuania and Sweden, 1977-94

ured in Stockholm. Blood was drawn into prechilled tubes coated with ethylenediaminetetra-acetic acid (EDTA), kept cool on ice, and centrifuged after 120 minutes at 4°C. Samples were stored in a dark refrigerator at 4°C. Samples from Vilnius were sent every week to Linköping as express cool packages (4°C). Both sets of samples were always analysed together in random and blinded order. Thus temperatures and times were the same for samples from the two centres.

The volunteers came to the hospitals between 0730 and 0900 after having fasted and abstained from smoking for 12 hours. The morning dose of prescribed drugs was taken. We measured their body weight, height, sagittal diameter of the abdomen, and girth of waist, thigh, and hip.[11 12] Blood pressure was measured twice using a mercury manometer, pulse rate was measured once after resting supine for 5 minutes, and a blood sample was taken. Smoking, alcohol, and physical activity were recorded by questionnaires. Work and leisure time physical activity were coded according to a four point scale.

Biochemical analyses

Cholesterol and triglyceride concentrations were analysed by enzymatic calorimetric methods (monotest cholesterol CHOD-PAP and triglycerides GPO-PAP; Boehringer Mannheim, Germany).

Lipoproteins containing apolipoprotein B were precipitated with phosphotungstic acid and magnesium ions and the cholesterol concentration in the solution was regarded as high density lipoprotein cholesterol. Low density lipoprotein cholesterol was calculated.[13] Apolipoprotein A I and B were measured by a rocket electroimmunoassay.[14] Lp(a) lipoprotein was estimated by an enzyme linked immunosorbent assay (ELISA) (TintEliza, Biopool, Sweden).

The susceptibility of low density lipoprotein to oxidation was measured as described by Kleinveld *et al.*[15] Each time two or three samples from each city that had been taken on the same day were analysed together, the time between blood sampling and analysis being eight days. Low density lipoprotein (0.75 ml) was dialysed against 3 litres of phosphate buffer 0.01 mmol/l, which had a pH of 7.4, contained sodium chloride 0.16 mmol/l, chloramphenicol 0.1 g/l, and EDTA 10 μmol/l, and was continuously bubbled through with nitrogen gas. After 20 hours of dialysis the lipoprotein was filtered (pore size 0.45 μm) and diluted in phosphate buffer that did not contain EDTA to a concentration of protein of 25 μg/ml. Total protein concentration was determined by the Lowry method with bovine albumin as the protein standard. Oxidation was initiated by copper sulphate 5 μmol/l, and its kinetics were monitored every two minutes as the change in absorbency at a wavelength of 234 nm at 30°C on a spectrophotometer (Beckman DU 640) equipped with a six position automatic sample changer. Lag phase in minutes was defined as the time between the addition of copper ions to the low density lipoprotein sample and the time point when the slope during the propagation phase reached baseline absorbency. The interassay coefficient of variation was 5%.

Resistance to oxidation in whole serum (serum lag phase) was determined according to the method of Regnström *et al.*[7] Serum was diluted to 0.67% (volume for volume) with phosphate buffer that did not contain EDTA. The change in absorbency at a wavelength of 234 nm was monitored every two minutes for four to five hours after the addition of copper sulphate (final concentration 50 μmol/l). The serum lag phase was calculated in the same way as described above. The interassay coefficient of variation was less than 6%.

Plasma concentrations of the lipophilic antioxidants α and γ tocopherol and α and β carotene and lycopene were determined by reverse phase high performance liquid chromatography.[16] Concentrations of α and γ tocopherol were expressed relative to total triglyceride plus total cholesterol concentrations. Food intake was examined by 24 hour dietary recall.[17] Total and percentage energy from food constituents were calculated according to national food tables.[18 19] Twenty per cent of the volunteers were interviewed on a Monday and the others from Tuesday to Friday.

Statistical methods

We used the statistical package for social sciences (SPSS) for Macintosh 6 for statistical analyses. Student's *t* test was used to test differences between groups. Dichotomous data were tested by a χ^2 test. The Mann-Whitney U test was applied when the data had a skewed distribution, but it did not alter the test results in any substantial way. Thus, only the results from Student's *t* test are given in the tables. P values of 0.01 or less were regarded as significant. Multiple regression analysis was performed to study the dependence of lag phase on different variables.

Results

The participation rate was 83% in both cities. In Vilnius 109 men participated; 131 were invited, 18 did not answer, and four refused. In Linköping 101 men participated; 122 were invited, 16 did not answer, three refused, and two were excluded. The number of participants with a cardiovascular diagnosis was similar. In each city 10 men were receiving treatment for hypertension. Five men in Vilnius had had a myocardial infarction and one had had a stroke; the corresponding figures in Linköping were four and two respectively.

As shown in table 1, mean body weight did not differ between the men in the two cities, but men in Vilnius had a higher mean body mass index. However, abdominal sagittal diameter and the ratio of waist to hip girth did not differ between the groups. Systolic

Table 1 Numbers of participants with history of cardiovascular disease and diabetes

	Vilnius (n = 109)	Linköping (n = 101)
Hypertension	10	10
Myocardial infarction	5	4
Stroke	1	2
Diabetes	1	2

blood pressure was higher in the men from Vilnius, but diastolic blood pressures did not differ. The number of current smokers was similar. More men in Vilnius reported low rates of physical activity during leisure time, but there was no difference during work time. The total energy intake did not differ between the two groups (table 2). Men in Vilnius had a higher relative fat intake than those in Linköping. Energy contribution from alcohol was similar (table 3).

Mean total and low density lipoprotein cholesterol concentrations were lower in the men from Vilnius (table 4), and the mean ratio between low and high density lipoprotein and apolipoprotein B concentrations were insignificantly lower. Plasma triglycerides, high density lipoprotein cholesterol, and Lp(a) lipoprotein concentrations did not differ.

Men from Vilnius had an appreciably shorter lag phase for low density lipoprotein after oxidative stress (table 4). Figure 2 shows the cumulative distributions of the lag phase for low density lipoprotein; the whole distribution is moved towards shorter times in the Lithuanians. Lag phase in whole serum was also shorter in the men from Vilnius.

The plasma concentrations of fat soluble antioxidants are given in table 5. Plasma concentrations of β carotene, lycopene, and γ tocopherol (corrected for lipid concentration) were lower in the men from Vilnius; α carotene and α tocopherol corrected for lipid concentration did not differ between the two groups.

We studied the dependence of the lag phase on α and γ tocopherol, β carotene, lycopene, low density lipoprotein cholesterol, high density lipoprotein cholesterol, body mass index, energy percentage fat intake, systolic blood pressure, and city in a forward stepwise multiple regression model. The variables with independent significant explanatory relations to lag phase were α tocopherol, low density lipoprotein cholesterol, and city. R^2 for the equation was 0.30—that is, 30% of the variation in lag phase could be explained by these three factors. Thus after correction for α tocopherol and low density lipoprotein cholesterol concentration the difference between the cities was still significant by 10.3 (SE 1.8) minutes ($P < 0.001$).

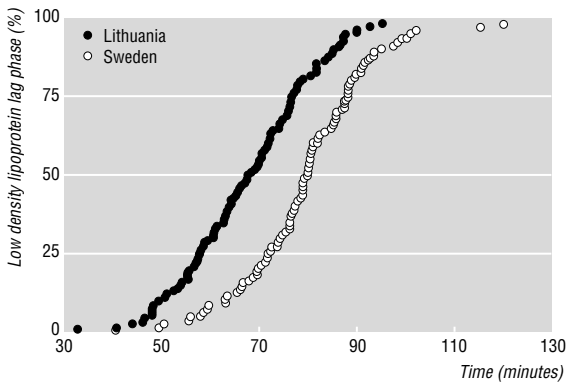

Fig 2 Cumulative distribution curves of lag phase for oxidation of low density lipoprotein in men from Vilnius and Linköping

Table 2 Anthropometric and lifestyle data on participants. Values are means (SE) unless stated otherwise

	Vilnius (n = 109)	Linköping (n = 101)	P value
Body weight (kg)	82.5 (1.2)	80.4 (1.2)	0.17
Height (cm)	175 (1)	178 (1)	<0.001
Body mass index (kg/m^2)	27.0 (0.3)	25.4 (0.4)	<0.001
Waist girth (cm)	92 (1)	91 (l)	0.40
Waist/hip ratio	0.92 (0.01)	0.91 (0.01)	0.14
Sagittal diameter (cm)	21.2 (0.3)	21.2 (0.3)	0.97
Blood pressure (mm Hg):			
Systolic	141 (2)	133 (2)	<0.01
Diastolic	88 (1)	86 (1)	0.27
Heart rate (beats/minute)	64 (1)	62 (1)	0.21
Alcohol (g/week)	97 (16)	88 (10)	0.84
No (%) of current smokers	39 (36)	27 (27)	0.15
Amount of tobacco smoked (g/day)	17 (2)	18 (2)	0.41
No (%) with low physical activity:			
During leisure time	43 (40)	18 (18)	<0.001
During work time	43 (40)	42 (42)	0.74

Table 3 Energy intake from major nutrients according to 24 hour recall. Values are mean (SE) percentages of total energy intake unless stated otherwise

	Vilnius (n = 109)	Linköping (n = 101)	P value
Mean (SE) total energy intake (MJ)	9.9 (0.4)	9.9 (0.3)	0.37
Fat	43.7 (1.1)	35.2 (0.7)	<0.001
Carbohydrate	42.1 (1.1)	46.3 (0.8)	<0.001
Protein	12.8 (0.3)	15.3 (0.3)	<0.001
Alcohol	3.0 (0.6)	3.1 (0.5)	0.04

Table 4 Plasma lipid and lipoprotein concentrations, lag phase of low density lipoprotein and total serum. Values are means (SE)

	Vilnius (n = 109)	Linköping (n = 101)	P value
Total cholesterol (mmol/l)	5.10 (0.09)	5.49 (0.10)	<0.01
Triglycerides (mmol/l)	1.46 (0.13)	1.52 (0.12)	0.35
Cholesterol (mmol/l):			
HDL	1.14 (0.03)	1.12 (0.03)	0.79
LDL	3.30 (0.09)	3.68 (0.10)	<0.01
LDL/HDL	3.11 (0.12)	3.50 (0.14)	0.04
Apolipoprotein A I (g/l)	1.33 (0.02)	1.30 (0.02)	0.42
Apolipoprotein B (g/l)	1.17 (0.03)	1.28 (0.03)	0.02
Lp(a) lipoprotein (mg/l)	200 (23)	177 (20)	0.91
Lag phase (minutes):			
LDL	67.6 (1.3)	79.5 (1.3)	<0.001
Serum	156.6 (3.9)	171.0 (3.8)	<0.01

HDL = high density lipoprotein.
LDL = low density lipoprotein.

Table 5 Mean (SE) plasma concentrations of lipid soluble antioxidant vitamins

	Vilnius (n = 100)	Linköping (n = 95)	P value
α Carotene (nmol/l)	80.8 (5.3)	84.8 (7.9)	0.32
β Carotene (nmol/l)	377 (20)	510 (33)	<0.01
Lycopene (nmol/l)	327 (22)	615 (32)	<0.001
α Tocopherol (μmol/mmol)*	3.3 (0.1)	3.4 (0.1)	0.35
γ Tocopherol (μmol/mmol)*	0.25 (0.01)	0.46 (0.02)	<0.001

*Concentrations were divided by plasma concentrations of cholesterol and triglycerides.

Discussion

We studied comparatively small, randomly selected and homogeneous population samples in two coun-

tries by using identical methods concomitantly. This approach has previously shown significant differences in the distribution of risk factors which could help to explain mechanisms behind observed differences in mortality from coronary heart disease between populations.[20-22]

The differences in traditional risk factors in the men from Vilnius and Linköping were small. This is in agreement with the World Health Organisation's monitoring trends and determinants in cardiovascular disease study (MONICA) performed in 1983-6, which showed that Lithuanian men from Kaunas had higher body mass index and moderately higher systolic blood pressure than Swedes from Gothenburg, whereas plasma cholesterol concentrations and smoking habits were similar.[23] In addition, the Kaunas-Rotterdam intervention study showed that in 1972-4 Lithuanian men had a more advantageous cardiovascular risk profile with less smoking, lower cholesterol concentration, and higher rates of physical activity than Dutch men.[5] Obviously, data from these two studies could not predict the dramatic increase in mortality from coronary heart disease in Lithuania over the past 10 years.

Two major findings

A striking finding in our study was the lower resistance of low density lipoprotein to oxidation in men from Vilnius. Several studies have suggested that low density lipoprotein may be oxidised in the arterial wall and thus initiate and promote atherosclerosis.[6] A short lag phase for the oxidation of low density lipoprotein is associated with coronary atherosclerosis in patients with coronary heart disease.[7 9] Susceptibility of low density lipoprotein to oxidation has been related to progression of atherosclerosis in carotid and femoral arteries, and a higher proportion of partially oxidised low density lipoprotein was found in patients with progression of atherosclerotic plaques.[8]

Another finding of interest was the lower plasma concentrations of β carotene, lycopene, and γ tocopherol in men from Vilnius. No difference was found in the mean concentrations of α tocopherol corrected for lipid concentrations. The relevance of these findings is supported by a recent study showing that Swedish men with coronary heart disease had reduced serum concentrations of γ tocopherol but not α tocopherol.[24] Furthermore, in a European multicentre case-control study of patients with coronary heart disease the mean β carotene concentration in adipose tissue was significantly lower in cases, but no difference was found in α tocopherol concentration.[10] However, Riemersma *et al* found that plasma concentrations of vitamin E were independently and inversely related to the risk of angina.[25] The health professionals follow up study found that high intakes of vitamin E were associated with decreased rates of coronary heart disease only when the high concentrations were obtained through dietary supplements such as vitamin pills.[26] In line with this, it was recently shown in English patients with coronary heart disease that 400 to 800 IU daily of α tocopherol decreased the number of cardiovascular deaths and non-fatal infarctions by 47% after a mean follow up of 510 days.[27]

Some studies support the view that β carotene has a protective role in coronary heart disease. A case-control study showed an increased risk of subsequent myocardial infarction with low concentrations of β carotene in blood samples drawn 7-14 years before the infarction.[28] Furthermore, a 12 year follow up study found that mortality from cardiovascular disease was correlated to low baseline concentrations of β carotene.[29] In the health professionals follow up study β carotene intake was associated with a lower risk of coronary heart disease among current smokers.[26] On the other hand, two recent interventional studies with β carotene treatment for up to 12 years did not show any effect on cardiovascular disease.[30 31]

Relation between lag phase and serum vitamins

The dependence of lag phase on antioxidants and other factors in a multiple regression model showed that 30% of the variability in the lag phase could be explained by α tocopherol and low density lipoprotein cholesterol concentrations. Furthermore, the city also contributed to the explanation, indicating that other factors that we did not measure are also important. The dependence of lag phase on α tocopherol concentration was unexpected as the two populations did not differ in the lipid adjusted concentrations of this antioxidant. However, α tocopherol was the most abundant lipid soluble antioxidant in all of the men and should therefore have an impact on the susceptibility of low density lipoprotein to oxidation. As only part of the lag phase was explained by the measured variables, other hitherto unknown factors must account for the difference in lag phase between the cities.

The finding of lower antioxidant concentrations in Vilnius may reflect differences in dietary habits between the two populations. Unfortunately, the food tables used in Lithuania are not reliable enough to determine the intake of micronutrients and the type of fat. Men in Vilnius got more of their energy from fat than did the men in Linköping, but their total and low density lipoprotein cholesterol concentrations were lower, which may indicate a higher intake of polyunsaturated fatty acids.[32] Kardinaal *et al* showed that low concentrations of β carotene in adipose tissue are particularly related to risk of coronary heart disease when intakes of polyunsaturated fatty acids are high.[33] This favours the view that the low concentrations of β carotene found in Lithuania may be a risk factor.

Conclusion

In conclusion, the results from our study suggest that traditional risk factors cannot explain the recent large increase in mortality from coronary heart disease in Lithuania compared with Sweden. The suggestion recently put forward that mechanisms other than traditional risk factors are responsible for the diverging trends in coronary heart disease in eastern and western Europe[4] is in line with our results. The differences in lag phase of low density lipoprotein oxidation and plasma concentrations of lipid soluble antioxidant vitamins in randomly selected Lithuanian and Swedish men are similar to differences recorded in men with and without coronary heart disease. This leads to the hypothesis that the increase in coronary heart disease in Lithuania may be related to the antioxidant status.

Key messages

- Mortality from coronary heart disease in 50-54 year old men is four times higher in Lithuania than in Sweden
- Differences in traditional risk factors for coronary heart disease in 50 year old men in Linköping (Sweden) and Vilnius (Lithuania) were small—systolic blood pressure was higher in men from Vilnius, but total and low density lipoprotein cholesterol concentrations were lower and smoking habits similar
- The resistance of low density lipoprotein to oxidation was lower in men from Vilnius and remained after adjustment for antioxidant vitamin concentrations
- Plasma concentrations of the antioxidant vitamins, β carotene, lycopene, and lipid adjusted γ tocopherol were lower in men from Vilnius; α tocopherol did not differ
- Mechanisms related to antioxidant state may be important in explaining the much higher mortality from coronary heart disease in Lithuanian compared with Swedish middle aged men

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Conflict of interest: None.

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ONE HUNDRED YEARS AGO

Doctors and fishermen

Francois Coppee has called the attention of the public in France to a strange arrangement in the French fishing fleets. By the law of their country French shipwrights and sea captains are bound to see that every kind of craft that sails with a crew of over twenty men carries a medical officer. Very large smacks, well known to British tourists, especially artists, put to sea for Iceland and Newfoundland in considerable fleets every season. The shipwright or owner, obliged to conform to the law, but unwilling to pay for a "useless pair of arms," demands that each doctor should help the fishermen to cut up and salt the fish. M. Coppee states that at Granville, Paimpol, and Fecamp, as many doctors as are wanted can be found only too ready to accept these terms. They must resemble the "experienced surgeon" of bygone days who, with "a cow," figured on advertisements of the sailings of British emigrant ships. (*BMJ* 1897;i:421.)

Vitamin C deficiency and risk of myocardial infarction: prospective population study of men from eastern Finland

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Abstract

Objective: To examine the association between plasma vitamin C concentrations and the risk of acute myocardial infarction.
Design: Prospective population study.
Setting: Eastern Finland.
Subjects: 1605 randomly selected men aged 42, 48, 54, or 60 who did not have either symptomatic coronary heart disease or ischaemia on exercise testing at entry to the Kuopio ischaemic heart disease risk factor study in between 1984 and 1989.
Main outcome measures: Number of acute myocardial infarctions; fasting plasma vitamin C concentrations at baseline.
Results: 70 of the men had a fatal or non-fatal myocardial infarction between March 1984 and December 1992. 91 men had vitamin C deficiency (plasma ascorbate <11.4 μmol/l, or 2.0 mg/l), of whom 12 (13.2%) had a myocardial infarction; 1514 men were not deficient in vitamin C, of whom 58 (3.8%) had a myocardial infarction. In a Cox proportional hazards model adjusted for age, year of examination, and season of the year examined (August to October *v* rest of the year) men who had vitamin C deficiency had a relative risk of acute myocardial infarction of 3.5 (95% confidence interval 1.8 to 6.7, $P = 0.0002$) compared with those who were not deficient. In another model adjusted additionally for the strongest risk factors for myocardial infarction and for dietary intakes of tea, fibre, carotene, and saturated fats men with a plasma ascorbate concentration <11.4 μmol/l had a relative risk of 2.5 (1.3 to 5.2, $P = 0.0095$) compared with men with higher plasma vitamin C concentrations.
Conclusion: Vitamin C deficiency, as assessed by low plasma ascorbate concentration, is a risk factor for coronary heart disease.

Introduction

The oxidation of low density lipoprotein has been implicated in atherogenesis and in the progression of early atherosclerotic plaques.[1-3] Experiments in rabbits have shown that atherogenesis can be inhibited by supplementation with antioxidants.[1 4-7] Epidemiological follow up studies suggest that a high intake of vitamin E might be associated with a reduced risk of coronary events.[8 9] Increased body stores of the transition metals iron and mercury, which catalyse lipid peroxidation, have been associated with excess risk of myocardial infarction.[10-12]

We found that a high titre of autoantibodies against oxidised low density lipoprotein was associated with accelerated progression of carotid atherosclerosis in a prospective nested case-control study.[13] Consistently, associations have been reported between raised titres of antibodies against oxidised low density lipoprotein[14] and reduced resistance to oxidation of low density lipoprotein[15] and increased severity of atherosclerosis. Vitamin C is an important water soluble dietary antioxidant in humans. We previously reported an association between low plasma vitamin C concentrations and enhanced progression of atherosclerosis.[16] Only a few studies have investigated the relation between the use of vitamin C supplements, dietary intake of vitamin C, or plasma vitamin C concentration and the risk of coronary disease, and their results are inconsistent.[3] None of them has considered the role of vitamin C deficiency.

We investigated the association of vitamin C deficiency with the risk of myocardial infarction in middle aged men free of coronary disease from eastern Finland, a population with low average vitamin C concentrations and high mortality from coronary heart disease.

Subjects and methods

The Kuopio ischaemic heart disease risk factor study is a population study designed to investigate risk factors for cardiovascular diseases, atherosclerosis, and related outcomes in men from eastern Finland.[18] The baseline examinations were carried out between March 1984 and December 1989. The study sample included 3235 eligible men aged 42, 48, 54, or 60 at the baseline examination; 2682 (82.9%) participated. Men with symptomatic coronary heart disease ($n = 92$) or ischaemia on maximal exercise testing ($n = 359$),[19] or both ($n = 585$), were excluded from the current analyses. Of the remaining 1646 men, 1605 had data on plasma ascorbate concentration at baseline.

The examination protocol and measurements have been described.[10-13] Plasma ascorbate concentrations were determined by a chromatographic method in deep frozen samples, which were stabilised in 5% metaphosphoric acid immediately after sampling.[20] The coefficient of variation between 12 batches was 7.2%.[20]

Plasma ascorbate concentration was redetermined in a subsample of 401 men with hypercholesterolaemia in samples drawn 4-9 years after the baseline examination. Pearson's correlation between the baseline and the remeasurement values was 0.27. Plasma vitamin C concentration below <11.4 μmol/l (2.0 mg/l) was defined as being at high risk of developing clinical symptoms of hypovitaminosis C and is considered to be a limit for vitamin C deficiency.[21 22] For these reasons we used this limit as the primary cut off value for plasma vitamin C concentration.

The main lipoprotein fractions were separated from fresh serum samples by ultracentrifugation and precipitation.[23] The cholesterol and triglyceride contents of all lipoprotein fractions were measured enzymatically. Serum apolipoprotein B concentration was determined by an immunoturbidimetric method.[12] Serum copper concentration was determined with an atomic-absorption spectrometric technique.[24] Plasma

fibrinogen concentration was determined on the basis of clotting of diluted plasma with excess thrombin.[12] Hair mercury content was measured with a flow injection and amalgam system (FIAS-200) in a Perkin Elmer Zeeman 5000 Spectrometer (Norwalk, CT).[12]

The consumption of foods was assessed when blood was sampled by recording intake over four days with a questionnaire, which was checked at interview.[25] The use of vitamin C tablets and vitamin C containing nutritional supplements was assessed in a self administered questionnaire.

The number of cigarettes, cigars, and pipefuls of tobacco currently smoked daily, the duration of regular smoking in years, and the history of myocardial infarction, angina, and other ischaemic heart disease were recorded using a self administered questionnaire, which was checked by an interviewer. A family history of coronary disease was defined as positive when the biological father, mother, sister, or brother of a subject had myocardial infarction, angina, or ischaemic heart disease.

The lifelong exposure to smoking (cigarette pack years) was estimated as the product of the number of years spent smoking and the number of tobacco products smoked daily at the time of examination. The consumption of alcohol in the previous 12 months was assessed with the Nordic alcohol consumption inventory, which contains 15 items.[26] Socioeconomic status was measured with a summary index that combined measures of income, education, occupation, occupational prestige, standard of living, and housing conditions.[27] Leisure time physical activity was assessed over the previous 12 months.[28]

Resting blood pressure was measured by one nurse with a random zero mercury sphygmomanometer.[10 12] The mean of six systolic pressure values was used in these analyses. Respiratory gas exchange was measured breath by breath with the MGC 2001 system (Medical Graphics, Minneapolis, MI) during a symptom limited exercise test.[19] Ischaemia in exercise electrocardiograms was coded manually by one cardiologist.[10 12] Diabetes was defined as either previous diagnosis of diabetes mellitus or fasting blood glucose concentration >8.0 mmol/l.

Acute myocardial infarctions in the cohort were monitored by a registry that collected detailed diagnostic information of all such attacks in the study cohort in a prospective manner.[29 30] Between March 1984 and December 1992 a fatal or non-fatal myocardial infarction was registered in 70 of the 1605 men at risk. The follow up period for individual subjects was up to 8.75 years, and the mean follow up time was about five years.

Risk factors for myocardial infarction were analysed using SPSS Cox proportional hazards models.[31 32] All tests of significance were two sided. Relative hazards adjusted for risk factors (risks) were estimated as the antilogarithm of a coefficient for independent variables. Their confidence intervals were estimated with a macro based on the assumption of asymptotic normality of estimates.

Results

Plasma ascorbate concentration ranged from 1.7 μmol/l to 137 μmol/l, with a mean (SD) of 47.7 (23.3) μmol/l. There was a slow average increase in the mean plasma ascorbate concentration during the six years of baseline examinations (46.0, 43.2, 43.7, 49.4, 56.8, and 48.3 μmol/l; $r = 0.12$, $P<0.0001$ for linear trend). For this reason the year of examination was adjusted for in all statistical analyses.

Table 1 Major coronary risk factors in men with and without vitamin C deficiency. Values are means (SE) unless stated otherwise

Characteristic	Plasma ascorbate ≤11.4 μmol/l (n = 91)	Plasma ascorbate >11.4 μmol/l (n = 1514)	P value*
Age (years)	54.7 (0.42)	52.1 (0.14)	<0.001
Smoking (No of pack years)	18.9 (2.2)	7.0 (0.4)	<0.001
No (%) of smokers	57 (63)	424 (28)	<0.001
Adulthood socioeconomic group (0-26)†	9.92 (0.37)	7.76 (0.11)	<0.001
Maximal oxygen uptake (ml/min/kg)	29.5 (0.6)	32.6 (0.2)	<0.001
Dietary carotene (μg/day)	1226 (110)	2723 (86)	<0.001
Examination in August to October (%)	6 (3)	30 (1)	<0.001
Blood leucocyte count ($\times 10^9$/l)	6.2 (0.2)	5.6 (0.0)	0.001
Dietary iron (mg/day)	16.8 (0.7)	18.9 (0.1)	0.004
Moderate to vigorous physical activity during leisure time (kJ/day)	144 (24)	214 (7)	0.005
Systolic blood pressure (mm Hg)	139 (2)	133 (0)	0.021
Alcohol intake (g/week)	116 (18)	72 (3)	0.019
Coffee intake (g/day)	645 (34)	562 (7)	0.019
Serum LDL cholesterol (mmol/l)	4.18 (0.12)	3.98 (0.03)	0.099
Serum apolipoprotein B (g/l)	1.06 (0.03)	1.03 (0.01)	0.126
Diabetes (%)	6.6 (2.6)	2.9 (0.4)	0.168
No (%) of men with rural place of residence	31 (34)	413 (27)	0.188
Hair mercury content (μg/g)	1.69 (0.16)	1.89 (0.05)	0.233
Dietary polyenes (g/day)	12.3 (0.6)	13.0 (0.1)	0.303
Dietary monoenes (g/day)	35.4 (1.1)	35.6 (0.3)	0.819
Serum triglycerides (mmol/l)	1.26 (0.07)	1.24 (0.02)	0.846
Serum HDL cholesterol (mmol/l)	1.31 (0.03)	1.32 (0.01)	0.941

LDL = low density lipoprotein.
HDL = high density lipoprotein.
*For difference in means; based on *t* tests allowing for unequal within group variances.
†High value denotes low socioeconomic status.

Plasma ascorbate concentration decreased with increasing age ($r = -0.17$). The age specific plasma ascorbate mean concentrations were 55.7, 52.3, 44.3, and 46.6 μmol/l for those aged 42, 48, 54, and 60, respectively ($P<0.0001$ for linear trend). Of dietary factors, only the intake of fruits and berries ($r = 0.276$) and of vegetables ($r = 0.255$) had any notable adjusted correlations with plasma ascorbate concentration. Plasma ascorbate concentration also correlated with the dietary intake of carotenes ($r = 0.159$) and the sum of C_{14} to C_{16} saturated fatty acids ($r = -0.096$). Men with plasma vitamin C concentrations <11.4 μmol/l differed from men with higher plasma vitamin C concentrations in many respects (table 1). Men deficient in vitamin C were older, had smoked more in their life time, and were in lower socioeconomic groups; they also had lower maximal oxygen uptake, lower dietary carotene intake, a higher blood leucocyte count, lower dietary iron intake, less moderate to vigorous physical activity during leisure time, higher systolic blood pressure, higher alcohol intake, and higher coffee consumption.

Men who had vitamin C deficiency (plasma ascorbate <11.4 μmol/l) were at an increased risk of myocardial infarction in the subsequent years (table 2). The relative risk for this lowest category compared with the highest and after adjustment for age, season, and year of examination was 4.0 (95% confidence interval

Table 2 Relative risks (95% confidence intervals) of myocardial infarction in 1605 men according to plasma vitamin C concentration at baseline

Plasma vitamin C (μmol/l)	Adjusted for age, season, and examination year	Adjusted for risk factors in table 3
<11.4	4.03 (1.74 to 9.36)	2.08 (0.82 to 5.30)
11.4-32.9	1.46 (0.71 to 3.01)	0.87 (0.40 to 1.87)
33.0-49.9	0.95 (0.42 to 2.12)	0.62 (0.26 to 1.45)
50.0-64.8	1.08 (0.49 to 2.38)	0.92 (0.41 to 2.07)
>64.8	1.00	1.00

1.7 to 9.4; P = 0.0012). There were no differences in the risk in the quarters of vitamin C concentration above this limit (table 2). Of 91 men with vitamin C deficiency, 12 (13.2%) had a myocardial infarction during the follow up, compared with 58 (3.8%) of the 1514 men with higher vitamin C concentrations (P = 0.00037, Fisher's exact test). The proportions of men with infarction in all categories from the lowest to the highest was 12 out of 91, 21 out of 382, 12 out of 383, 13 out of 376, and 12 out of 373 (P = 0.0013 for linear trend in proportions).

The strongest predictors of acute myocardial infarction after adjustment only for age (in years), year of examination (covariates for individual years), and season of the year (August to October *v* the rest of the year) in this study cohort were maximal oxygen uptake (inversely), the number of pack years smoked, blood leucocyte count, and low plasma ascorbate concentration (table 3). Serum apolipoprotein B, plasma fibrinogen, serum copper, and triglyceride concentrations, hair mercury content, blood haemoglobin concentration, systolic blood pressure, diabetes, moderate to vigorous physical activity during leisure time (inversely), serum high density lipoprotein-2 cholesterol concentration (inversely), family history of coronary disease, and low socioenonomic group were also significantly associated with the risk of myocardial infarction. Men who had vitamin C deficiency (plasma ascorbate concentration <11.4 μmol/l) had a 3.5-fold (1.8 to 6.7, P = 0.0002) risk of myocardial infarction after adjustment for age, season, and year of examination (table 3).

To estimate the independent impact of risk factors, all factors shown in table 3, as well as age, year of examination, season, and three dietary factors, were entered simultaneously in a Cox proportional hazards model. In this multivariate model only the number of cigarette pack years smoked, low plasma vitamin C concentration, family history of coronary heart disease, low maximal oxygen uptake, and high hair mercury content (in the order of strength) had significant associations with infarction risk (table 3). When all risk factors shown in table 3, as well as dietary intakes of tea, fibre, and saturated fats, were allowed for, men with plasma ascorbate concentrations <11.4 μmol/l had a relative risk of myocardial infarction of 2.5 (1.3 to 5.2, P = 0.0095) compared with those with higher plasma ascorbate concentrations.

Only 89 (5.5%) of our study subjects took supplements containing vitamin C. The exclusion of these men did not materially change the results. In fact, among the 1516 men who had not used vitamin C containing supplements during the previous week the relative risk for having a plasma ascorbate concentration <11.4 μmol/l was 3.7 (1.9 to 7.2, P = 0.0001) after adjustment for age, season, and year of examination. The use of vitamin C supplements had no significant association with the risk of myocardial infarction.

Discussion

Vitamin C as an antioxidant

Ascorbate is considered to be the most effective antioxidant in human plasma,[33] and vitamin C inhibits the oxidation of low density lipoprotein in vitro.[17 34-36] Ascorbic acid is the first antioxidant to be used up during lipid peroxidation in plasma, and detectable lipid peroxidation starts only after all ascorbate has been

Table 3 Strongest risk factors for acute myocardial infarction in 1605 men who were free of coronary heart disease

Risk factor*	Mean or proportion (SD)	Range	Adjusted relative risk (95% CI)†	P value	Relative risk (95% CI)‡	P value
Pack years of smoking	7.6 (15.5)	0 - 144	1.52 (1.32 to 1.76)	< 0.0001	1.40 (1.15 to 1.70)	0.0008
Maximal oxygen uptake (ml/min×kg)	32.5 (7.0)	6.4 - 65.4	0.56 (0.43 to 0.73)	< 0.0001	0.65 (0.47 to 0.92)	0.0137
Blood leucocyte count (10^9/l)	5.6 (1.6)	2.4 - 18.9	1.53 (1.30 to 1.79)	<0.0001	1.16 (0.93 to 1.44)	0.2015
Plasma vitamin C (<2.0 mg/l *v* >2.0 mg/l)	5.7%	0 -1	3.49 (1.82 to 6.69)	0.0002	2.55 (1.26 to 5.17)	0.0095
Serum apolipoprotein B (g/l)	1.0 (0.2)	0.01 - 1.9	1.49 (1.20 to 1.86)	0.0003	1.29 (1.01 to 1.66)	0.0454
Plasma fibrinogen (g/l)	2.96 (0.53)	1.32 - 6.71	1.35 (1.10 to 1.65)	0.0038	0.99 (0.76 to 1.30)	0.9477
Serum copper (mg/l)	1.10 (0.17)	0.50 - 1.91	1.33 (1.08 to 1.64)	0.0080	0.99 (0.76 to 1.28)	0.9125
Serum triglycerides (mmol/l)	1.24 (0.74)	0.18-10.93	1.24 (1.04 to 1.47)	0.0148	1.12 (0.88 to 1.43)	0.3543
Hair mercury (>2.0 μg/g *v* <2.0 μg/g)	33.6%	0 - 1	1.78 (1.10 to 2.87)	0.0184	1.68 (1.01 to 2.81)	0.0448
Blood haemoglobin (g/l)	147 (9)	105 - 234	1.31 (1.04 to 1.64)	0.0219	1.17 (0.90 to 1.52)	0.2463
Systolic blood pressure (mm Hg)	134 (16)	88 - 213	1.28 (1.04 to 1.58)	0.0224	1.14 (0.91 to 1.43)	0.2560
Diabetes (yes *v* no)	3.1%	0 - 1	2.81 (1.12 to 7.08)	0.0279	2.05 (0.77 to 5.44)	0.1502
Moderate to vigorous physical activity during leisure time (kJ/day)	210 (260)	0 - 3803	0.66 (0.46 to 0.960	0.0289	0.80 (0.57 to 1.13)	0.2079
Serum HDL_2 cholesterol (mmol/l)	0.87 (0.28)	0.09 - 2.77	0.74 (0.57 to 0.97)	0.0298	0.95 (0.69 to 1.31)	0.7638
Family history of coronary heart disease (yes *v* no)	44.4%	0 - 1	1.67 (1.04 to 2.68)	0.0326	1.86 (1.14 to 3.02)	0.0129
Low socioeconomic status in adulthood (0-26)	7.9 (4.2)	0 - 18	1.28 (1.01 to 1.64)	0.0492	1.06 (0.81 to 1.40)	0.6622
Dietary carotene intake (g/day)	2.6 (3.3)	0.03 - 60.6	0.69 (0.45 to 1.05)	0.0835	0.86 (0.57 to 1.32)	0.4984
Body mass index (kg/m^2)	26.7 (3.5)	18.8 - 48.6	1.17 (0.94 to 1.45)	0.1545	0.96 (0.74 to 1.24)	0.7640

HDL = high density lipoprotein.
*Risk factors, apart from four categorical risk factors (plasma vitamin C, hair mercury, diabetes, and family history of coronary heart disease) were entered in SD scale. Relative risks are per SD unit.
†Adjusted for age, season, and year of examination.
‡All risk factors shown were entered simultaneously in model, which also included age, season, year of examination, and intakes of tea, fibre, and saturated fats.

completely used up; researchers have even suggested that only ascorbate can prevent the initiation of lipid peroxidation.[17 33 36]

Ascorbate is an important physiological antioxidant that helps to regenerate reduced antioxidative tocopherol from the tocopheroxyl radical.[35 36] Although it is not lipid soluble, ascorbate could theoretically also inhibit lipid peroxidation through this mechanism. Retsky and Frei have suggested that vitamin C spares, rather than regenerates, α tocopherol and other endogenous antioxidants when low density lipoprotein is exposed to copper ions and that ascorbic acid can terminate lipid peroxidation, thereby protecting partially oxidised low density lipoprotein against further oxidative modification.[39] Vitamin C's inhibition of lipid peroxidation in vivo has not, however, yet been confirmed in supplementation studies in humans.

Vitamin C and blood pressure

Vitamin C deficiency was associated in our study with raised blood pressure. There is some evidence in favour of a role of oxidative stress in the aetiology of hypertension.[40] We observed in a population study an association between lowered plasma concentrations of ascorbic acid and raised resting blood pressure both in normotensive and in hypertensive men.[41]

In a small clinical trial to investigate the effect of antioxidant supplementation on blood pressure in 40 middle aged men the mean systolic blood pressure decreased by 12.5 (SE 2.5) mm Hg in the supplemented group and by 5.2 (1.9) mm Hg in the placebo group ($P = 0.027$ for difference).[42] In addition, the reduction in blood pressure correlated strongly with the increase in plasma ascorbic acid concentration.[42]

Vitamin C and coronary heart disease

In a prospective population study, the national health and nutrition examination survey epidemiologic follow up study, men and women with the highest vitamin C intakes (>50 mg/day and regular vitamin C containing supplements) had lower coronary mortality than subjects with the lowest vitamin C intake (by 45% and 25%, respectively).[44] In the health professionals' follow up study and in the nurses' health study the use of vitamin C supplements was not significantly associated with the risk of coronary events,[8 9] although there was a non-significant trend towards a reduced risk among those taking supplements.

In the 12 year follow up of the prospective Basel study a low plasma concentration of both vitamin C (<22.7 μmol/l) and carotene (<0.23 μmol/l) was associated with a twofold increase in the risk of coronary heart disease ($P = 0.022$).[45 46] The excess mortality from heart disease associated with low plasma ascorbate concentration alone was not, however, significant in this study of 2974 Swiss men with comparatively high average antioxidant intakes.

In a Finnish study a low dietary intake of vitamin C was associated with increased coronary mortality among women but not among men in a cohort of 5133 Finns who did not have heart disease and were followed up for 14 years.[47] In a 20 year follow up study in Britain by Gale *et al* of 730 elderly men and women who were free of major cardiovascular disease at baseline the mortality from cerebrovascular stroke was highest in those with the lowest vitamin C intake.[48] People in the highest third of plasma vitamin C concentration had a 30% reduced risk of stroke compared with those in the lowest third after adjustment for a number of cardiovascular risk factors. No association was found between vitamin C concentration and mortality from coronary heart disease.[48]

Key messages

- This study shows that vitamin C deficiency may be associated with an increased risk of myocardial infarction
- The findings also provide additional support for the role of oxidative stress and lipid peroxidation in coronary heart disease
- Although deficiency in vitamin C may increase coronary risk, this study does not provide evidence in favour of the benefit of vitamin C supplements

Riemersma *et al* observed an association between low plasma concentrations of vitamin C and an increased risk of angina in a population based case-control study.[49] The unadjusted risk was 2.4 in the lowest fifth of plasma vitamin C concentration (<13.1 μmol/l). This odds ratio was weakened to 1.6 and was not significant when smoking and other coronary risk factors were adjusted for.

Confounding is a major problem in all non-experimental studies of associations between nutrient intakes and the risk of disease. An important potential source of bias in studies of the association between plasma vitamin concentrations or the use of supplements and the risk of coronary heart disease are other differences between people with a low and a high intake of vitamins. Although people taking vitamin supplements are generally more health conscious than others, those with a vitamin deficiency may be ill or have detrimental health habits. We tried to assess differences between subjects with low and high plasma ascorbate concentrations in every respect that was relevant to coronary risk. However, some unmeasured factors might have counfounded the relation between vitamin C concentration and risk of infarction or the statistical control for confounding may not have been perfect because of imprecision in measurement or an imperfect fit of the model used. Plasma concentration of vitamin C varied considerably with season within subjects. This variability was most probably random and thus was likely to attenuate the observed relation with risk of infarction. It also implies that a single measurement of plasma vitamin C concentration may classify subjects incorrectly and may be insufficient for clinical practice.

Common to all previous prospective studies is a narrow range and a high overall population concentration of vitamin C. We previously reported that the average plasma ascorbate concentration is comparatively low in eastern Finnish men and that during winter it falls below the limit of deficiency (2.0 mg/l).[22]

To our knowledge, our current results are the first empirical evidence in humans to show that vitamin C deficiency, as measured by low plasma ascorbate

concentration, is a risk factor for coronary heart disease. In our cohort plasma vitamin C concentration above the limit of deficiency was not associated with the risk of acute myocardial infarction. Thus, high intakes of vitamin C or vitamin C supplements would probably not reduce the risk of acute myocardial infarction. Our findings suggest, instead, that if a minimal necessary requirement of vitamin C is not met the risk of myocardial infarction is increased.

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First myocardial infarction in patients of Indian subcontinent and European origin: comparison of risk factors, management, and long term outcome

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Abstract

Objectives: To compare long term outcome after first myocardial infarction among British patients originating from the Indian subcontinent and from Europe.
Design: Matched pairs study.
Setting: Coronary care unit in central Leicester.
Subjects: 238 pairs of patients admitted during 1987-93 matched for age (within 2 years), sex, date of admission (within 3 months), type of infarction (Q/non-Q), and site of infarction.
Main outcome measures: Incidence of angina, reinfarction, or death during follow up of 1-7 years.
Results: Patients of Indian subcontinent origin had a higher prevalence of diabetes (35% *v* 9% in patients of European origin, $P < 0.001$), lower prevalence of smoking (39% *v* 63%, $P < 0.001$), longer median delay from symptom onset to admission (5 hours *v* 3 hours, $P < 0.01$), and lower use of thrombolysis (50% *v* 66%, $P < 0.001$). During long term follow up (median 39 months), mortality was higher in patients of Indian subcontinent origin (unadjusted hazard ratio = 2.1, 95% confidence interval 1.3 to 3.4, $P = 0.002$). After adjustment for smoking, history of diabetes, and thrombolysis the estimated hazard ratio fell slightly to 2.0 (1.1 to 3.6, $P = 0.02$). Patients of Indian subcontinent origin had almost twice the incidence of angina (54% *v* 29%; $P < 0.001$) and almost three times the risk of reinfarction during follow up (34% *v* 12.5% at 3 years, $P < 0.001$). The unadjusted hazard ratio for reinfarction in patients of Indian subcontinent origin was 2.8 (1.8 to 4.4, $P < 0.001$). Adjustment for smoking, history of diabetes, and thrombolysis made little difference to the hazard ratio. Coronary angiography was performed with similar frequency in the two groups; triple vessel disease was the commonest finding in patients of Indian subcontinent origin and single vessel disease the commonest in Europeans ($P < 0.001$).
Conclusions: Patients of Indian subcontinent origin are at substantially higher risk of mortality and of further coronary events than Europeans after first myocardial infarction. This is probably due to their higher prevalence of diffuse coronary atheroma. Their need for investigation with a view to coronary revascularisation is therefore greater. History of diabetes is an inadequate surrogate for ethnic origin as a prognostic indicator.

Introduction

Migrants to the United Kingdom from the Indian subcontinent have a higher mortality from coronary heart disease than the indigenous population.[1] In Britain there are 1.6 million people of Indian subcontinent origin, and the effect of demographic change is likely to amplify the public health impact of this increased risk of coronary heart disease during the next two decades.[2] The greater incidence of acute myocardial infarction is associated with high prevalence of diabetes mellitus,[3 4] and patients of Indian subcontinent origin with coronary heart disease are more likely than Europeans to have diffuse coronary atheroma at angiography.[5-7]

Relatively little is known about the clinical course of myocardial infarction in patients of Indian subcontinent origin, though a greater prevalence of triple vessel disease suggests that there might be a higher risk of recurrent coronary events. Two studies have reported that clinical outcome and long term survival were not significantly different in patients of Indian and European origin[5 8]; a third study has found increased early mortality after first myocardial infarction in patients of Indian origin.[9] We compared clinical characteristics and outcome in a large consecutive series of patients of Indian subcontinent origin and matched patients of European origin who were followed up for one to seven years after first myocardial infarction.

Many migrants of South Asian origin, a large proportion having come from East Africa, settled in Leicester from the early 1970s onwards. They now form 23% of the population of the city. The largest ethnic subgroup is Gujarati speaking. The migrant group is substantially younger than the indigenous population,[2] and its distinctive epidemiological characteristics (notably a higher prevalence of non-insulin dependent diabetes mellitus and ischaemic heart disease) have been reported elsewhere.[10]

Methods

Patients—For all patients admitted to the coronary care unit of Leicester Royal Infirmary, a standard dataset is collected and entered on a computer database. From this we identified all patients of Indian subcontinent origin admitted with confirmed acute myocardial infarction between January 1987 and August 1993, by surname analysis.[11] The diagnosis required at least two of three factors: (i) a typical history of cardiac pain not relieved by rest or nitrates; (ii) evolving electrocardiographic changes compatible with the diagnosis; (iii) a rise in serum cardiac enzymes to greater than twice the upper limit of the laboratory reference range. For each patient identified, a patient of European origin meeting the same diagnostic criteria was matched by age (within two years), date of admission (within three months), sex, and type (Q/non Q) and site of infarction. It was not possible to match six patients, and a further four were lost to follow up. The analysis includes 241 matched pairs (200 men and 41 women).

Data—The standard clinical data set was collected prospectively, validated by a single investigator before

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Table 1 Clinical characteristics, management, and coronary angiography in patients of Indian subcontinent and of northern European origin. Values are numbers (percentages) unless specified otherwise

	Indian origin (n=241)	European origin (n=341)	Odds ratio (95% CI)	P value
Mean age (years)	57.6	57.6		
Smokers	94 (39)	151 (63)	0.4 (0.2 to 0.5)	<0.001
Known diabetes	84 (35)	21 (9)	5.6 (3.4 to 9.2)	<0.001
Known hypertension	56 (23)	37 (15)	1.4 (0.8 to 2.4)	>0.05
Missed diagnosis	40 (17)	15 (6)	4.3 (2.1 to 8.6)	<0.001
Thrombolysis given	121 (50)	160 (66)	0.5 (0.3 to 0.7)	<0.001
Median time from onset (hours)	5	3		<0.01
In hospital mortality	10 (4)	8 (3)	1.3 (0.5 to 3.5)	>0.05
Left ventricular failure in coronary care unit	73 (30)	52 (22)	1.3 (0.9 to 2.0)	>0.05
Exercise stress test	143 (59)	162 (67)	0.8 (0.5 to 1.2)	>0.05
Coronary angiography:	86 (36)	112 (47)		
3 Vessel disease	44 (51)	24 (21)		
2 Vessel disease	27 (31)	39 (35)	χ^2=22, df=2, P<0.0001	
0-1 Vessel disease	15 (18)	49 (41)		
Coronary angioplasty	22 (9)	40 (17)	0.6 (0.3 to 1.4)	>0.05
Coronary artery grafting	42 (17)	51 (21)	0.8 (0.5 to 1.3)	>0.05

computer entry, and not subsequently modified. It comprised details of clinical presentation, medical history and coronary risk factors, treatment, complications, and acute outcome. To this was subsequently added information on events after discharge including reinfarction and cardiac investigations (exercise stress testing, coronary angiography, coronary angioplasty, and coronary artery bypass grafting). Data sources included general practitioner records, hospital notes, stress test registers, and catheter laboratory logs at the adjacent cardiothoracic centre which provides all invasive cardiology services for the district. Angiograms were coded (blind to ethnic origin) as one, two, or three vessel coronary disease. Reinfarction was accepted to have occurred only on the evidence of a diagnosis at discharge from hospital. Deaths were ascertained from the NHS central register.

Statistical analysis—Categorical variables were analysed with McNemar's test for matched data or by χ^2 tests where the matched design was broken. Distribution of survival times was compared by using Kaplan-Meier plots and tested by the generalised Savage (Mantel-Cox) method. A Cox proportional hazards model was fitted in which potential confounding variables were fitted as covariates. Matching was taken account of by fitting a stratified model.[12]

Results

Clinical characteristics and inpatient course

Route of admission was similar in both groups: 77 (32%) of north European patients and 68 (28%) of patients of Indian subcontinent origin were admitted directly from a general practitioner referral; the remaining patients in both groups were admitted from the casualty department. Patients of Indian subcontinent origin had the expected lower prevalence of smoking and higher prevalence of diabetes (table 1).[4 9] As noted in an earlier study, their delay from onset of symptoms was significantly longer, the diagnosis of myocardial infarction was less commonly made at presentation, and consequently the use of thrombolysis was lower in this group.[13] In addition to delay the other main reason for the disparity in thrombolysis rates was a greater rate of missed diagnosis in patients of Indian subcontinent origin (34% *v* 19%, P = 0.001). Contraindication to thrombolysis was higher in the north European group (21% *v* 7%, P = 0.001). Highest recorded serum creatine kinase concentration was slightly higher in patients of Indian subcontinent origin (median 1789 *v* 1523 IU/l, P = 0.09). However, the incidence of early complications (left ventricular failure, hypotension, or tachyarrhythmia) did not differ significantly.

Mortality and morbidity during long term follow up

Diagnosis of angina during follow up was more common in patients of Indian subcontinent origin than in Europeans (54% *v* 29%, P < 0.001), as was rate of reinfarction (34% *v* 12.5% at 3 years, P < 0.0001) (fig 1). The increased tendency to reinfarction in patients of Indian subcontinent origin may be partly or fully attributable to ethnic differences in the risk factor profile. To take account of this, a Cox proportional hazards model was fitted in which variables that were different in the two groups (family history of coronary heart disease under the age of 50 years, use of thrombolytic drugs, maximum blood glucose concentration in hospital, smoking, and known diabetes) were fitted as covariates. Matching was taken account of by fitting a stratified model. The unadjusted hazard ratio for reinfarction in patients of Indian subcontinent origin was 2.76 (95% confidence interval 1.75 to 4.36, P < 0.001). Addition of these variables made little difference to the estimated hazard ratio (adjusted hazard ratio = 3.0, 1.7 to 5.3, P < 0.001). The observed ethnic difference in risk could therefore not be explained by these risk factors. The proportional hazards assumption was checked and found to be valid.

Survival after first myocardial infarction was also poorer in patients of Indian subcontinent origin (fig 2). The unadjusted hazard ratio was 2.12 (1.33 to 3.37, P = 0.002); after adjustment for the same variables used in the reinfarction model, the estimated hazard ratio fell slightly to 2.0 (1.1 to 3.6, P = 0.025).

Diagnostic procedures and revascularisation

The two ethnic groups did not differ significantly in the use of exercise stress testing, coronary angioplasty, or coronary artery bypass grafting (table 1). Rates of positive results on stress testing were similar in the two ethnic groups (62% in patients of Indian subcontinent

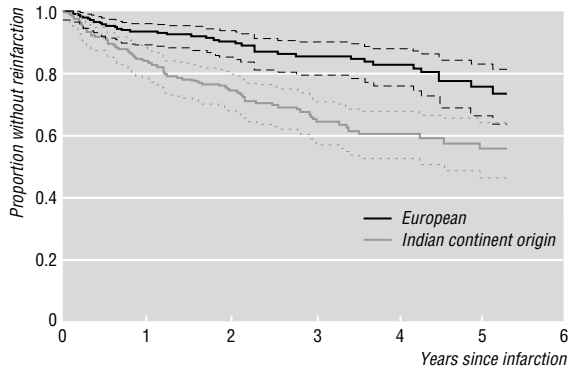

Fig 1 Reinfarction after first myocardial infarction in patients of Indian subcontinent and of European origin

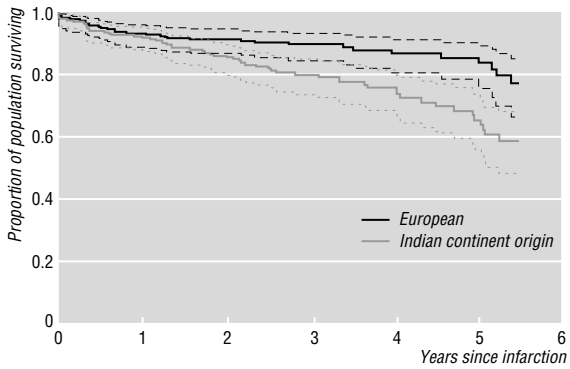

Fig 2 Survival after first myocardial infarction in patients of Indian subcontinent and of European origin

origin and 51% in patients of European origin). The distribution of coronary angiography over time after first infarction showed no difference in the use of this procedure in the first six months, but subsequently it tended to be used less in patients of Indian subcontinent origin despite their higher reinfarction rate. At angiography (table 1), triple vessel disease was strikingly more common in patients of Indian subcontinent origin, whereas single vessel disease was the most likely finding among Europeans (51% *v* 41%; $P < 0.0001$).

Discussion

These data provide the largest and longest age controlled comparative analysis of the outcome of myocardial infarction in patients of Indian subcontinent origin so far published. Patients of Indian subcontinent origin presented later and gave rise to more diagnostic difficulty than European patients. In consequence, thrombolytic treatment was less likely to be used.

Ethnic differences in mortality and reinfarction

Although the most recent study found a significant increase in early mortality in patients of Indian subcontinent origin after myocardial infarction,[9] two previous studies found no such ethnic difference in mortality or in reinfarction. The first study included 77 white patients and 54 patients of Indian subcontinent origin, the latter predominantly Gujaratis (as in the present study).[5] No age adjustment was made in the analysis, although the patients of Indian subcontinent origin were considerably younger. Coronary angiography was performed within three months of infarction in 62 European patients and 41 patients of Indian subcontinent origin. European patients had a significantly lower prevalence of triple vessel disease and significantly lower atheroma scores in vessels not associated with the infarct territory. Of the 113 patients followed up at one year, 71% of European patients and 58% of patients of Indian subcontinent origin were alive and had had no further cardiac events (difference not significant).

The second study analysed 102 matched pairs of patients of Indian subcontinent and European origin admitted to Birmingham hospitals with first myocardial infarction.[8] Matching factors were age, sex, time, and season of infarction. The proportions in each ethnic group surviving to one, two, three, and four years were not significantly different (though there was a trend to lower survival in patients of Indian subcontinent origin). The smaller sample size and less efficient statistical analysis of survival (contrasting simple proportions rather than distributions of survival times), both reducing statistical power, may account for the different conclusions drawn in this study and in ours. The fact that this longer term study found a substantial ethnic effect raises the possibility that the risk associated with Indian subcontinent origin is a late effect. However, a late effect was not apparent from the survival curves, which start to diverge immediately after infarction. This, and the fact that the hazard ratio associated with ethnic origin seems to be constant, suggests an immediate and sustained effect on risk of reinfarction.

Diabetes and coronary angiography

It is well recognised that patients of Indian subcontinent origin with myocardial infarction have a greater prevalence of diabetes.[4 5 14 15] Diabetic patients in general tend to have more diffuse coronary artery disease than non-diabetic patients and a higher mortality after infarction. Wilkinson *et al* found that controlling for a history of diabetes removed much of the excess early mortality risk in patients of Indian subcontinent origin.[9] This was not our finding: controlling for diabetes had little effect on the hazard ratio for both mortality and reinfarction. Hughes *et al* found no difference in atheroma score in the coronary arteriograms of patients of Indian subcontinent origin who were normoglycaemic and of those who had impaired glucose tolerance or diabetes (6.2 (SD 4.9) *v* 5.7 (3.9), $P > 0.8$).[5] The practical implication is that patients of Indian subcontinent origin with first myocardial infarction, regardless of a history of diabetes, are more likely than European patients to have triple vessel disease. This should be considered when deciding on the need for coronary angiography.

The use of coronary angiography was slightly (though not significantly) lower among patients of Indian subcontinent origin than European patients in

Key messages

- The cumulative incidence of reinfarction after a first myocardial infarct is threefold higher in patients of Indian subcontinent origin than in European patients
- Patients of Indian subcontinent origin have poorer survival after first myocardial infarction
- The commonest coronary angiographic finding in patients of Indian subcontinent origin is triple vessel disease
- A history of known diabetes is not in itself an adequate marker of adverse prognosis in this ethnic group
- After myocardial infarction, patients of Indian subcontinent origin have a high risk of recurrent myocardial ischaemia and an increased likelihood of needing coronary revascularisation

our study, whereas the angiographic findings and prognostic difference indicate that the reverse should have been the case. The reasons are unclear. It has previously been reported that referral and investigation for angina are relatively delayed in patients of Indian subcontinent origin despite more extensive coronary atheroma at presentation.[6 13]

Implications

The age distribution of the population with Indian subcontinent origin in the United Kingdom is younger than that of the indigenous population. Demographic shift alone will increase the public health impact of the increased incidence of coronary heart disease in the former group in the coming decades.[2]. In the absence of any proved primary preventive strategy to mitigate the influence of ethnic origin on risk, it is particularly important that optimum secondary preventive care is achieved. Revascularisation by coronary artery bypass grafting improves survival among patients with triple vessel disease,[16] and therefore accurate identification of such patients should be given a high priority.

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No sex differences in immunisation rates of British south Asian children: the effect of migration?

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In most countries male mortality exceeds female mortality at every age. In parts of northern Africa, the Middle East, and the Indian subcontinent, however, where life expectancy is relatively low, female mortality at 0-4 years exceeds that of males.[1] Discrimination against girls in India is blatant in the selective abortion of female fetuses.[2] Girls also have poorer access to health services than boys: in Bombay boys have immunisation rates 16% higher than girls.[3] We do not know whether these sex differences in health service uptake occur in British residents whose ethnic origins lie in the Indian subcontinent (south Asians). To answer this question we conducted a historical cohort study comparing immunisation uptake in south Asian and European children living in Newcastle.

Methods and results

South Asian populations in Newcastle—Of the 259 541 residents of Newcastle at the 1991 census, 2176 reported their ethnic origin as Indian, 2913 as Pakistani, and 1300 as Bangladeshi. About half of Newcastle Indians and Pakistanis and 30% of Bangladeshis were born in the UK. Most Pakistanis and Bangladeshis are Moslem and live in the economically disadvantaged "west end" of Newcastle. Most Indians are Hindus and Sikhs and are more widely dispersed.

The study investigated the uptake of complete courses of triple vaccine; measles, mumps, and rubella vaccine; and BCG immunisation in the first two years of life, as recorded by the Newcastle child health register. The family health services authority register recorded 12 867 children born in Newcastle from 1 January 1989 to 28 February 1993—that is, after the introduction of measles, mumps, and rubella immunisation in 1988 and old enough to have received it by the start of data collection on 1 March 1995. A name search identified 346 Moslem south Asians and 115 Hindus and Sikhs who were matched for age, sex, and general practitioner to 461 children of European origin. The power of this study to detect a 16% sex difference in immunisation rate (as reported by Naik[3]) was 99%. The Mann-Whitney test was used to compare differences in age at immunisation; 95% confidence intervals were calculated for differences in immunisation rate.

Table 1 shows no important sex differences in immunisation uptake for any ethnic group. Only one of the 24 comparisons of immunisation uptake by sex was significantly different (measles, mumps, and rubella in non-Moslem south Asians; 95% confidence

Table 1 Immunisation uptake and age on completion of immunisation course, by ethnic group and sex. Results are % uptakes for each immunisation course (and median age at completion)

	South Asian: Moslem		South Asian: Non-Moslem		All South Asians		European comparison group	
Immunisation	Boys (n = 182)	Girls (n = 164)	Boys (n = 55)	Girls (n = 60)	Boys (n = 237)	Girls (n = 224)	Boys (n = 237)	Girls (n = 224)
Measles, mumps, and rubella	94 (1.04)	94 (1.05)	100 (1.06)	93 (1.03)	95 (1.05)	94 (1.05)	90 (1.04)	90 (1.05)
Tetanus	93 (0.49)	91 (0.55)	91 (0.46)	92 (0.45)	92 (0.48)	91 (0.52)	88 (0.42)	89 (0.44)
Polio	94 (0.49)	89 (0.55)	91 (0.42)	90 (0.45)	93 (0.47)	89 (0.52)	88 (0.42)	88 (0.44)
Pertussis	91 (0.49)	89 (0.55)	89 (0.43)	85 (0.44)	90 (0.48)	88 (0.51)	82 (0.42)	80 (0.43)
Diptheria	85 (0.48)	85 (0.53)	85 (0.43)	82 (0.45)	85 (0.47)	84 (0.51)	88 (0.42)	87 (0.45)
BCG	60 (0.01)	64 (0.01)	51 (0.02)	55 (0.01)	58 (0.01)	62 (0.01)	2 (0.01)	6 (0.10)

interval for the difference between boys and girls: 0 to 13%). Median age at completion of immunisation was generally higher in girls, but the differences were small and not significant.

Comment

Overall, rates of immunisation uptake were high for all groups of children. Indeed, as in Glasgow,[4] south Asians in Newcastle had higher immunisation rates than Europeans. There are two alternative explanations for the lack of sex differences in this study. Firstly, it is possible that no sex differences would have existed in this population of south Asians if they had not migrated. Secondly, and plausibly, migration may have been a factor in eliminating behaviour which determines sex differences. Free medical care in Britain and the relative affluence of life in Newcastle compared with the Indian subcontinent may have played a part. If so, sex differences on the Indian subcontinent might be expected to disappear as health services improve and populations become more affluent. Nevertheless, sex differences in the Indian subcontinent are seen where women have low status, even in wealthy families and when medical care is free.[5] Absence of sex differences in Newcastle south Asians may therefore reflect changes in culture as well as in material circumstances. While this interpretation warrants debate, our findings suggest that sex differences in health care use in British south Asian children are absent or insignificant and provide hope that such differences on the Indian subcontinent are amenable to change.

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Use of calcium antagonists and need for perioperative transfusion in older patients with hip fracture: observational study

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Calcium antagonists inhibit platelet aggregation,[1] which may increase the risk of bleeding.[2] Whether these drugs increase postsurgical haemorrhage remains controversial,[3] but more attention is being given to reducing surgical bleeding because of the risks associated with homologous transfusions.[4] We evaluated the haemorrhagic potential of calcium antagonists in hip surgery, which is associated with considerable transfusion requirements.

Patients, methods, and results

We prospectively evaluated the need for perioperative transfusion in 161 consecutive elderly patients with hip fracture (mean (SE) age 80 (0.5) years; 82% women) who had cemented total hip arthroplasty (85 subjects), hemiarthroplasty (16), or osteosynthesis (60) in 1994-5. One hundred patients had hypertension, 19 diabetes, 47 vascular disease, six liver disease, and 17 peptic disease. Nitrates were taken by 56 patients, angiotensin converting enzyme inhibitors by 44, digitalis by 39, diuretics by 45, and corticosteroids by nine. Seventy patients took calcium antagonists (50 nifedipine; 14 amlodipine; 6 nimodipine) at home and throughout their hospital stay.

All patients received diazepam and atropine as premedicants. Anaesthesia was induced with thiopentone and vecuronium and maintained with nitrous oxide, isoflurane, and fentanyl. Intraoperative arterial blood pressure was maintained within 20% of preinduction values. Crystalloid and colloid were infused at a standardised rate. Packed cell volume was determined at 30 minute intervals during surgery; hae-

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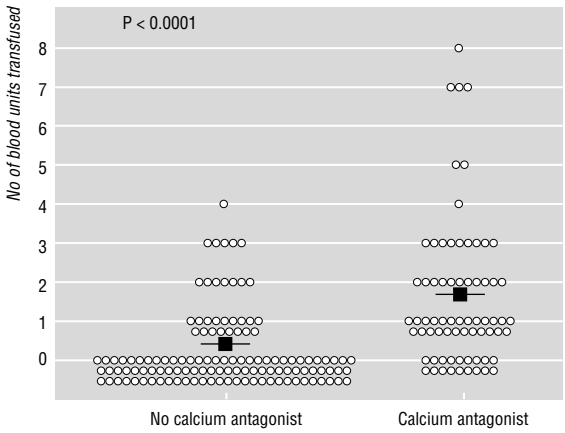

Fig 1 Number of transfused blood units according to use of calcium antagonists. P value was calculated by the Kruskal-Wallis H test. Full squares represent the mean number of transfused blood units

moglobin concentrations were determined preoperatively, at the end of surgery, the next morning, and after one week. Allogenic packed red blood cells were administered as required in single units, either intraoperatively to maintain a minimum packed cell volume of 28% or postoperatively to achieve a minimum haemoglobin concentration of 95 g/l.[4] No patients received scavenged red cells. Subcutaneous heparin and intravenous ketorolac were started on admission.

Transfusions were required in 52 (74%) patients taking calcium antagonists, but only 30 (33%) of the remaining subjects ($P<0.0001$; fig 1); the mean (SE) number of units received were 1.7 (0.22) and 0.9 (0.10) respectively ($P<0.0001$). Among patients who did not receive transfusions, the fall in haemoglobin concentration after surgery was greater in patients taking calcium antagonists than in other patients. (24.2 (3) *v* 13.6 (1.5) g/l after 24 hours and 33.5 (3.2) *v* 18.6 (1.7) g/l after one week, $P<0.005$). Patients taking calcium antagonists showed increased prevalence of hypertension (90% (63) *v* 41% (37); $P<0.001$) and vascular disease (43% (30) *v* 19% (17); $P<0.002$) and higher blood pressure (152 (2) *v* 142 (2) mm Hg; $P<0.002$) than the other patients. Other demographic, clinical, laboratory (including clotting), and surgical parameters showed no variation with use of calcium antagonists.

After hypertension, vascular diseases, and other variables associated with the outcome (age, sex, preoperative haemoglobin concentration, and type and duration of surgery) were adjusted for, Cox regression analysis gave the risk of transfusion associated with calcium antagonists as 2.05 (95% confidence interval 1.14 to 3.70). The population attributable risk of receiving transfusions for calcium antagonists was 24%. When only patients with hypertension ($n=100$) were included the adjusted relative risk for calcium antagonists was 2.35 (1.15 to 4.78). No dose related gradient was found. When specific drugs were examined separately similar risks were found for those taking nifedipine (relative risk = 2.67; 95% confidence interval 1.24 to 5.75), and amlodipine (2.36; 1.30 to 4.28) as in non-users. Too few patients took nimodipine for analysis.

Comment

Our findings indicate that calcium antagonists are associated with increased perioperative transfusion requirements and postoperative haemoglobin loss. Calcium antagonists may have enhanced bleeding in our patients directly or through some interaction with ketorolac.[1 5] If an interaction existed this may explain the lack of a dose dependent effect.[2 5] Many strategies have been proposed to reduce surgical transfusion requirements and ensuing morbidity.[4] Our results suggest that switching patients treated with calcium antagonists to alternative drugs before surgery might reduce by 24% the number of patients requiring transfusions.

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Vasospasm of the nipple—a manifestation of Raynaud's phenomenon: case reports

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Raynaud's phenomenon was first described by Maurice Raynaud in 1862. It is defined as intermittent ischaemia affecting the acral parts of the body, most commonly the fingers or toes. It is much more prevalent in women, with a female to male ratio of 9:1.[1] It is common in healthy women of childbearing age, affecting up to 22% of healthy women in the 21-50 year age group.[2]

Nipple pain is the most common symptom in breastfeeding women and is the second most common reason given for abandoning breastfeeding, exceeded only by perceived low milk supply.[3] We report on five women with Raynaud's phenomenon affecting their nipples.

Subjects and methods

Five breastfeeding patients presented to us in 1994-5 with signs and symptoms suggesting a diagnosis of Raynaud's phenomenon affecting their nipples (table

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Table 1 Characteristics of women with vasospasm of the nipple

Case No	1	2	3	4	5
Age	28	30	32	32	30
Smoking	No	No	No	No	No
Family history	No	Father	Mother (positive antinuclear antibody)	No	No
History of Raynaud's phenomenon before first pregnancy	No	Fingers and nipples	Fingers and nipples	No	No
Birth order of index child	2	2	2	1	2
Age of child when mother's symptoms started	1 Week	3 Weeks	2 Weeks	1 Week	1 Day
Nipple vasospasm with previous baby	4 Months; breastfed for 14 months	Stopped breastfeeding at 6 weeks because of pain	Breastfed for 7 months in spite of pain	Not applicable	No
Nipple pain during pregnancy	No	No	No	No	No
Nipple trauma	No	Cracked nipples both sides	Ulcer left nipple	Blistering both sides	Cracked nipples both sides
Nipple colour change	Triphasic	Triphasic	Biphasic (white and blue)	Biphasic (white and blue)	Biphasic (white and blue)
Screening tests for secondary Raynaud's phenomenon	Negative	Positive antinuclear antibody (titre 80, pattern speckled); rheumatoid factor activity 22 (<21)	C-reactive protein 24 mg/l (<9); erythrocyte sedimentation rate 39 mm/h (1-15); mild increase in α_2 globulins	Negative	Negative

1). The major presenting complaint of each of the five women was severe, debilitating nipple pain. Three of the patients had had identical pain when breastfeeding a previous child. One had abandoned breastfeeding at six weeks because of pain; the others had continued breastfeeding for 14 and for 7 months in spite of pain.

In each of these women, blanching of the nipple occurred not only during and immediately after feeds but also between feeds. Exposure to cold precipitated nipple blanching and pain in all patients. Two patients showed the classical triphasic colour change of Raynaud's phenomenon (white, blue and red) in their nipples, and three showed biphasic colour change (white and blue).

Two of the patients gave a history of Raynaud's phenomenon before their first pregnancy, affecting not only fingers and toes but also their nipples. Two gave a family history of Raynaud's phenomenon affecting a parent. None of the patients had any symptoms or signs to suggest a diagnosis of secondary Raynaud's phenomenon. None of the patients smoked. Four of the five patients reported nipple trauma (ulceration, cracking, and blistering) which proved difficult to heal.

The most common cause of nipple pain is poor positioning of the baby at the breast and/or poor attachment of the baby to the breast.[4] Poor positioning and attachment can also give rise to blanching of the nipple secondary to compression. All five patients were reviewed by at least one lactation consultant for optimal positioning and attachment of the baby to the breast. The patients' breasts and nipples and their babies' mouths were examined for any abnormalities that may have given rise to nipple pain or trauma. On the basis of presenting symptoms and signs and an absence of any other diagnosable cause for nipple pain, a diagnosis of Raynaud's phenomenon was made in all five women.

Comment

The concept of Raynaud's phenomenon occurring at sites other than the digits is not new. Vasospasm affecting coronary, gastrointestinal, genitourinary, and placental vasculature has been described in patients with Raynaud's phenomenon.[5] Breastfeeding may increase the risk of nipple vasospasm because the nipples are exposed and subject to mechanical stimulation during the breastfeeding process. Raynaud's phenomenon in breastfeeding women poses the dual problems of distressing pain in the patient combined with an increased risk of failure of breastfeeding.

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ONE HUNDRED YEARS AGO

Hampstead Heath in the jubilee year

We are glad to be able to state that the Home Office has decided that the cemetery which it proposed should be established in close proximity to Hampstead Heath is not to be allowed. We congratulate the thousands who use that beautiful open space, and, we may add, we congratulate ourselves, for the articles which appeared in the British Medical Journal were copied extensively or used by the press, and awakened public interest at a time when there was danger that the cemetery company would obtain their desire before the public had become aware of their intention. At this jubilee season, when national rejoicing is largely taking the form of personal pecuniary generosity, it would make for the national health and well-being if attention was directed to the further extension of those open spaces which are limited in area, as well as to the establishment of other and smaller spaces in the thickly populated quarters of our large towns. (*BMJ* 1897;i:864.)