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Serum sialic acid concentration and cardiovascular mortality

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Abstract

Objective—To determine whether serum sialic acid concentration may be used to predict short and long term cardiovascular mortality.

Design—Prospective study on all men and women who had their serum sialic acid concentration measured as part of a general health survey in 1964 or in 1965. All were followed up for an average of 20·5 years.

Setting—Geographical part of the county of Värmland, Sweden.

Subjects—Residents in the area participating in a health check up in 1964-5 (27 065 men and 28 037 women), of whom 372 men (169 with incomplete data and 203 lost to follow up) and 345 women (143 and 202 respectively) were excluded; thus 26 693 men and 27 692 women entered the study. The study sample was restricted to subjects aged 40-74 during any of the 20 years' follow up.

Main outcome measures—Serum sialic acid concentration, serum cholesterol concentration, diastolic blood pressure, body mass index at the general health survey visit; cardiovascular and non-cardiovascular deaths during three periods of follow up (0-6 years, 7-13 years, and 14-20 years), according to the Swedish mortality register, in subjects aged 45-74.

Results—Mean serum sialic acid concentration (mg/100 ml) was 68·8 (SD 8·0) for men and 69·2 (8·0) for women; the average concentration increasing with age in both sexes. A total of 5639 (21%) men and 3307 (12%) women died during the follow up period, in whom death in 3052 (54%) men and 1368 (41%) women was from cardiovascular causes. During short (0-6 years), medium (7-13 years), and long (14-20 years) term follow up the relative risk of death from cardiovascular disease increased with increasing serum sialic acid concentration. The relative risk (95% confidence interval) associated with the highest quartile of sialic acid concentration compared with the lowest quartile was 2·38 (2·01 to 2·83) in men and 2·62 (1·93 to 3·57) in women. Similar results were found for deaths from non-cardiovascular disease with relative risks of 1·50 (1·34 to 2·68) in men and 1·89 (1·57 to 2·28) in women, but these relative risks were significantly lower than those for deaths from cardiovascular disease (p<0·001 and p<0·005 respectively). In multivariate analysis of total mortality and of cardiovascular mortality with sialic acid concentration, serum cholesterol concentration, diastolic blood pressure, and body mass index as independent variables the impact of sialic acid concentration was virtually the same as in univariate analysis.

Conclusion—Serum sialic acid concentration is a strong predictor of cardiovascular mortality. A possible explanation of these findings is that the serum sialic acid concentration may reflect the existence or the activity of an atherosclerotic process, and this may warrant further investigation.

Introduction

Sialic acid, a family of acetylated derivatives of neuraminic acid, is widely distributed in mammals. It usually occurs as a terminal component at the nonreducing end of carbohydrate chains of glycoproteins

and glycolipids.[1] In human plasma a large quantity of sialic acid is found in orosomucoid, α_1 antitrypsin, haptoglobin, ceruloplasmin, fibrinogen, complement proteins, and transferrin.[2,3] Some of these sialylated glycoproteins are called acute phase reactants, and such substances rapidly increase in concentration after the onset of an inflammatory reaction or injury.[4]

A few earlier studies have investigated aspects of the relation between sialic acid concentration and cardiovascular disease. Succari et al[5] and Hrncir et al[6] found raised serum concentrations of sialic acid in patients with acute myocardial infarction. The sialic acid concentration is higher in subjects with diabetes than in those without diabetes[7] and in subjects with diabetic microangiopathies and macroangiopathies than in subjects with diabetes with no complications.[8] To our knowledge, however, no prospective studies have investigated the impact of serum sialic acid concentration on mortality from cardiovascular diseases.

The aim of this study was to investigate whether serum sialic acid concentration could be used as a predictor of cardiovascular mortality during short term and long term follow up of a general Swedish population.

Subjects and methods

STUDY POPULATION

During 1962-5 a general health survey was carried out among residents of a geographical part of the county of Värmland, Sweden.[9,10] All inhabitants aged 25 years or older were offered a medical check up, including measurement of blood pressure, height, and weight. Blood and urine tests were performed, one of which was the measurement of serum sialic acid concentration. As the method for serum sialic acid analysis was changed during 1963 we restricted our study to the population aged 25-74 screened in 1964 or in 1965. Altogether, 27 065 men and 28 037 women participated.

SCREENING PROCEDURES

About 15 ml of blood was taken from non-fasting subjects into two glass tubes and left to clot for an hour at room temperature. The samples were then centrifuged and aliquots of the serum decanted into disposable plastic containers. Samples chilled in ice were sent overnight to the laboratory for analysis. All chemical analyses were run on an automatic analyser (AutoChemist). Svennerholm's method was used to measure the serum sialic acid concentration,[11] and cholesterol was analysed according to a modified Liebermann-Burchard method described by Zak et al.[12] Diastolic blood pressure was measured to the nearest

TABLE II—*Number of person years generated during 20·5 years of follow up in men and women*

	Men	Women
Age (years) during follow up:		
45-54	122 116	126 975
55-64	120 946	128 208
65-74	86 481	100 482
Total	329 543	355 665

TABLE III—*Distribution of sialic acid concentration in participants of the survey. Figures are numbers (percentages)*

Sialic acid concentration (mg/100 ml)	Men	Women
≤54	54 (0·2)	39 (0·1)
55-59	1 617 (6·1)	1 475 (5·3)
60-64	5 644 (21·1)	5 478 (19·8)
65-69	7 207 (27·0)	7 470 (27·0)
70-74	5 485 (20·5)	5 704 (20·6)
75-79	3 597 (13·5)	3 930 (14·2)
80-84	2 046 (7·7)	2 419 (8·7)
85-89	581 (2·2)	683 (2·5)
90-94	239 (0·9)	275 (1·0)
95-99	118 (0·4)	120 (0·4)
≥100	105 (0·4)	99 (0·4)
Total	26 693	27 692

TABLE IV—*Numbers of participants and mean (standard deviation) sialic acid concentration by age*

Age (years)	Men		Women	
	No	Mean (SD) sialic acid concentration (mg/100 ml)	No	Mean (SD) sialic acid concentration (mg/100 ml)
25-29	2296	67·0 (7·05)	2541	67·4 (7·38)
30-34	2636	67·3 (6·81)	2815	67·0 (6·98)
35-39	2997	67·4 (7·31)	3140	67·2 (7·08)
40-44	3515	68·0 (7·39)	3498	67·6 (7·02)
45-49	3200	68·4 (7·66)	3141	68·1 (7·43)
50-54	3221	69·0 (7·89)	3310	69·7 (7·90)
55-59	3013	69·7 (8·29)	3209	70·7 (8·18)
60-64	2561	70·5 (8·69)	2679	71·8 (8·60)
65-69	1946	71·2 (8·94)	2011	72·8 (8·57)
70-74	1308	72·2 (9·22)	1348	74·0 (8·75)

5 mm Hg. Height was measured to the nearest centimetre and weight to the nearest kilogram. Data were incomplete or missing in 169 men and in 143 women, including a few subjects in whom the personal identification number was missing or uninterpretable.

MORTALITY DURING FOLLOW UP

The Swedish mortality register includes data on the cause of death in all subjects living in Sweden at the time of their death. We used this register, which has very few omissions,[13] to identify fatal events in our study cohort, and all deaths occurring during 1964-85 were considered in our analysis. The underlying cause of death is coded by trained staff according to the International Classification of Diseases, the seventh revision[14] being used for deaths occurring from 1964 to 1968 and the eighth revision[15] for deaths occurring in 1969 or later. In the seventh edition cardiovascular death is defined by the codes 330-334, 420, or 422 and in the eighth edition by the codes 410-413 or 430-438.

Survey participants recorded in the original survey register were linked to the mortality register and to the 1980 national census register to check for subjects lost to follow up. A survey participant missing from the two registers was categorised as lost to follow up and excluded from further analysis (203 men and 202 women).

Table I summarises the number, age, and sex of subjects who were excluded from the analysis of the study cohort. Data were complete for 98·8% of those subjects who originally participated in the survey

TABLE I—*Age, sex distribution and number of subjects excluded among survey participants in study cohort*

	Subjects excluded from survey		Residual survey participants	Study sample contributing to person years
	Data incomplete or missing	Lost to follow up		
Men				
Age (years):				
25-34	37	75	4 932	4 814
35-44	49	54	6 512	6 467
45-54	45	36	6 421	6 421
55-64	20	19	5 574	5 574
65-74	18	19	3 254	3 254
Total	169	203	26 693	26 530
Women				
Age (years):				
25-34	26	70	5 356	5 282
35-44	41	46	6 638	6 612
45-54	26	33	6 451	6 451
55-64	33	35	5 888	5 888
65-74	17	18	3 359	3 359
Total	143	202	27 692	27 592

(27 065 men and 28 037 women), altogether, corresponding to 78% of men and 81% of women of the total population at risk, based on the 1960 census.

Deaths occurring only between the ages of 45 and 74 years in subjects who were aged 25-74 at the time of the health examination were included in the analysis. Consequently, the study sample was restricted to those subjects who were aged 45-74 during any of the 20 years of follow up.

STATISTICAL METHODS

Quartiles of sialic acid concentration were determined for each five year age stratum at screening (25-29, 30-34, ... 70-74), and these age-adjusted quartiles formed the basis for further analysis. Mortality was standardised to the age distribution of the total follow up person years to give the mortality for each follow up period. Mortality during three follow up periods (0-6 years, 7-13 years, and 14-20 years) was calculated for each quartile of sialic acid concentration. Average

TABLE V — *Age standardised mortality per 1000 person years (number of deaths) by quartile interval of serum sialic acid concentration in subjects aged 45-74 at follow up*

Follow up (years)	Serum sialic acid concentration quartile			
	<1	1-2	2-3	3-4
Total mortality (men)				
0-6	12·6 (312)	12·9 (321)	16·3 (401)	23·7 (567)
7-13	14·6 (431)	15·0 (442)	18·0 (512)	23·2 (624)
14-20	13·1 (402)	16·8 (505)	17·5 (511)	23·1 (611)
Total mortality (women)				
0-6	7·5 (185)	7·5 (191)	9·9 (224)	14·6 (364)
7-13	7·2 (229)	7·4 (235)	9·8 (306)	12·6 (375)
14-20	6·8 (230)	8·0 (270)	9·4 (306)	12·1 (372)
Cardiovascular mortality (men)				
0-6	6·1 (150)	5·9 (148)	8·4 (205)	12·6 (299)
7-13	7·3 (218)	7·9 (232)	10·5 (298)	14·3 (384)
14-20	7·0 (219)	9·0 (270)	9·6 (280)	13·1 (349)
Cardiovascular mortality (women)				
0-6	2·7 (68)	2·7 (69)	3·8 (95)	6·4 (154)
7-13	2·9 (93)	2·8 (89)	3·9 (123)	5·9 (175)
14-20	2·5 (86)	3·3 (111)	4·2 (141)	5·3 (164)
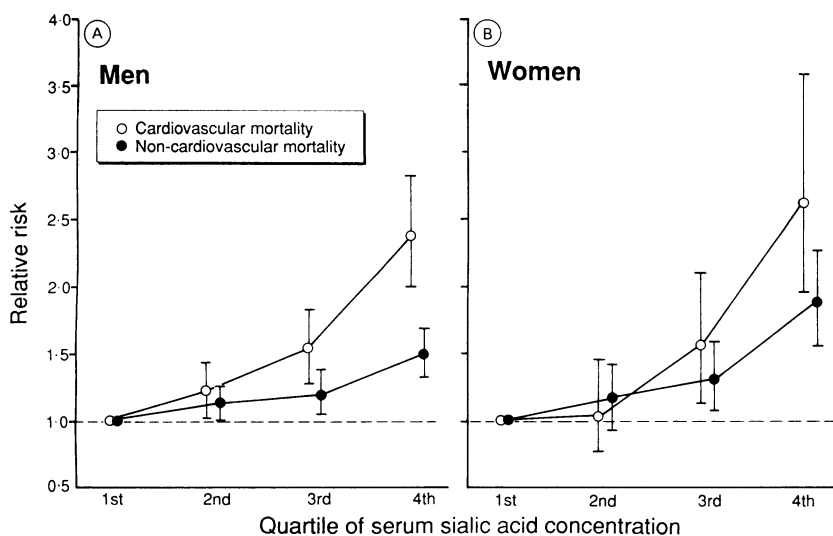
Age adjusted relative risks of cardiovascular and non-cardiovascular mortalities by quartile of serum sialic acid concentration among men (a) and women (b) aged 45-74 at follow up. Bars are 95% confidence intervals

TABLE VI — *Mean (standard deviation) diastolic blood pressure, total serum cholesterol concentration, and body mass index in men and women aged 25-74 and correlations of each variable with serum sialic acid concentration*

	Men		Women	
	Mean (SD)	Correlation	Mean (SD)	Correlation
Diastolic blood pressure (mm Hg)	87·3 (12·8)	0·14	89·0 (14·0)	0·22
Total serum cholesterol (mmol/l)	6·45 (0·96)	0·09	6·62 (1·05)	0·12
Body mass index (kg/m²)	25·1 (3·0)	0·11	24·9 (3·8)	0·24

follow up during the first year—that is, from the date of participation in the health examination to 31 December of the same year—was 0·55 years. The average follow up time was therefore 20·55 years. Statistical testing of relative risk estimates was performed with a weighted regression model. The best fit was achieved by assuming a normal error distribution for the logarithmic transformed rates. Number of person years was entered as weights in the computations (generalised linear interactive modelling (GLIM)[16]).

Body mass index was calculated as weight (kg)/ (height (m))².

Results

Of the 26 693 men and 27 692 women included for follow up, 163 men and 100 women died before the age of 45 and consequently did not contribute person years to this study (table I). The total cohort followed up comprised 329 543 person years for men and 355 665 person years for women (table II).

The mean serum sialic acid concentration was 68·8 (SD 8·0) mg/100 ml in men and 69·2 (8·0) mg/100 ml in women. Table III shows the distributions of serum sialic acid concentration for men and women. The distribution was skewed to the right for both sexes but was strictly unimodal like that of several other risk factors, such as blood pressure and serum cholesterol concentration. Table IV shows the mean (SD) serum sialic acid concentration by sex and by five year age group. It is evident that the average sialic acid concentration increased with age.

A total of 5639 (21%) men and 3307 (12%) women, died during follow up, in whom death in 3052 (54%) men and 1368 (41%) women was of cardiovascular origin. Increasing total mortality occurred from the lowest to the highest of the sialic acid concentrations in both men and women. After standardisation for age this pattern was virtually consistent among the three, seven year periods of short, medium, and long term follow up (table V). The same was true for cardiovascular mortality.

As only minor differences were found in mortality among the three periods of follow up and no interaction with age was found we considered it justifiable to merge the results for all the years when further analysing the data. The figure shows the relative risk for cardiovascular and non-cardiovascular mortality (total mortality minus cardiovascular mortality) during 0 to 20 years of follow up in men and in women. This relative risk increased for men, irrespective of the cause of death, from the lowest to all higher quartiles, but in women a significant increase was found only between the second and fourth quartiles compared with up to the first quartile. There was a significantly increasing trend for both sexes over all quartiles, irrespective of the cause of death (p<0·001 for cardiovascular deaths and p<0·001 for non-cardiovascular deaths in men, and p<0·001 for both in women). The relative risk for cardiovascular death increased significantly more when correlated with quartile of sialic acid concentration than did the risk for non-cardiovascular death in men (p<0·001) and in women (p<0·05).

MULTIVARIATE ANALYSIS

Table VI shows the mean diastolic blood pressure, total serum cholesterol concentration, and body mass index for men and for women. The correlations between sialic acid concentration and each of these risk factors for cardiovascular disease were generally low but significant for both sexes. In a multivariate analysis of cardiovascular mortality with sialic acid concentration, total serum cholesterol concentration, diastolic blood pressure, and body mass index as independent

variables the impact of sialic acid concentration changed only marginally compared with that shown for univariate analysis. For example, the relative risk between the third and fourth quartile of sialic acid concentration in men decreased from 2·38 to 2·07. The same was true for total mortality.

Discussion

A few case-control studies showed that serum sialic acid concentration is higher in patients with acute myocardial infarction[5 6] and have suggested that there is a lag between the acute event and the rising concentration.[6] These findings do not, however, justify any firm conclusions about the direction of the relation, that is, whether a high serum sialic acid concentration predicts future cardiovascular mortality or whether it is caused by the acute condition.

Our study showed a strong and consistent association between a single randomly measured serum sialic acid concentration and cardiovascular mortality during an average of 20·5 years of follow up in both men and women. The magnitude of the relative risk was similar to that for serum cholesterol concentration in this population,[17] and there was a clear and uniform dose-response relation. This relation may, however, have been caused by a confounder that is highly correlated to serum sialic acid concentration but was not controlled for in this study. The link between mortality and the sialic acid concentration measured on one occasion remained unchanged for several years. Such a potential confounder must therefore have remained active during a similarly extended time frame. None of the classic risk factors for cardiovascular disease that were controlled for in this study had a high enough correlation with sialic acid concentration to support this explanation. This was confirmed by results of the multivariate analysis.

There was a significant but weaker relation between serum sialic acid concentration and non-cardiovascular mortality. This may be explained either by a true causal relation, with the limitations described above for cardiovascular mortality, or by systematic misclassification of the cause of death—for example, in the case of multiple causes of death. Supporting the second explanation is the fact that this relation was equally consistent over the entire follow up period, which contradicts the suggestion that the risk related to higher concentrations of sialic acid reflects an acute phase activity—for example, in the case of an existing cancer.[18]

The reliability of a sialic acid concentration measured on one occasion can be affected firstly, by the precision of the test and by methods of analysis and, secondly, by short and long term intraindividual variability. These sources of error would all weaken the relation, as would errors resulting from random misclassification of the cause of death. Thus it is reasonable to assume that our results exist despite possible errors of measurement and classification and not because of them.

Smoking habit is an obvious possible confounder that we could not adjust for as data on tobacco consumption were not available. Krolikowski et al found that 20 non-smoking patients had marginally higher serum sialic acid concentrations than six patients who smoked,[19] but we are unaware of any other studies to investigate the link between serum sialic acid concentration and smoking. That study, though small, contradicted smoking as a confounder in this context. Other possible confounders are coagulation factors such as plasma fibrinogen, which is a recognised acute phase reactant and sialic acid carrier in plasma[2] that has been linked with cardiovascular

morbidity.[20-22] The triglyceride concentration also has to be considered as Radhakrishnamurthy et al found a moderately high correlation (r=0·42) between serum triglyceride concentration and serum sialic acid concentration in 65 patients with diabetes.[7] Further investigation of these possible sources of bias is therefore needed.

Many acute phase reactants contain sialic acid.[23] Taniuchi et al estimated a correlation of 0·9 between the serum concentrations of sialic acid and orosomucoid (a serum globulin) and concluded that the measurement of sialic acid in serum seemed to provide a rapid and simple index as acute phase reactants.[2] An increased concentration of acute phase reactants caused by an acute inflammatory disease or by an injury, however, cannot explain the constant excess mortality during the 20 years after the measurement of sialic acid concentration. Stuart et al have, however, shown a correlation between atherosclerotic peripheral vascular disease and serum globulin concentration.[24] Thus one possible explanation of our results might be that the serum sialic acid concentration reflects the existence or maybe even the activity of an atherosclerotic process, which in turn might cause a fatal cardiovascular event several years later.

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