PAPERS AND ORIGINALS

Raised Erythrocyte Sedimentation Rate in Asymptomatic Hyperlipidaemia

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Summary

In 101 subjectively healthy persons, who at a routine health examination were found to be markedly hyperlipidaemic, the erythrocyte sedimentation rate (E.S.R.) was significantly raised. The E.S.R. was raised above 25 mm/hr in 44, 64, and 23% respectively of subjects with type II A, II B, and IV hyperlipoproteinaemia in comparison to only 6% in sex- and age-matched normolipidaemic controls.

Several explanations for this E.S.R. elevation have been studied. The levels of plasma lipoproteins do not appear themselves to influence the E.S.R., as among other things there was no difference in plasma concentrations of cholesterol and triglycerides in hyperlipidaemic persons with high and low E.S.R. The concentration of lysolecithin, which may decrease the E.S.R. was the same in the hyperlipidaemic persons with high E.S.R. as in those with low. However, the incidence of ischaemic exercise E.C.G. changes was 38% in the hyperlipidaemic subjects with E.S.R. below 24 mm/hr and 72% in those with E.S.R. above 25 mm/hr. For the time being one possible reason for the raised E.S.R. thus seems to be that the hyperlipidaemia causes silent vascular disease that in its turn produces the E.S.R. elevations.

Introduction

Recent studies (Böttiger, 1973 a) have shown that not only plasma proteins but also lipids exert an influence on the erythrocyte sedimentation rate (E.S.R.), an influence previously found (Theorell, 1930) and denied (Ohlson and Rundquist, 1932). Further, it has been found (Böttiger and Carlson, 1972) that among persons in a prospective study that later developed myocardial infarction, the original E.S.R. values were higher in persons with high (above 330 mg/100 ml) than in those with low serum cholesterol values, and that the frequency of a slightly raised E.S.R. (> 10 mm/hr) was 65% in the former against only 30% in the latter group. Thus, an analysis of the E.S.R. in hyperlipidaemic subjects seemed justifiable.

A study in progress, involving the examining and following of otherwise healthy persons who at a routine health screening centre incidentally were found to be hyperlipidaemic, offered a unique opportunity to perform such an investigation.

Material and Methods

The Metropol Health Centre, Stockholm, performs regular health examinations at yearly intervals of employees of a number of companies. All subjects have a complete physical examination as well as urine analysis (protein and glucose) and a determination of haemoglobin and E.S.R. (Westergren method). Further, blood is taken for the analysis of serum lipids.

Persons who in all aspects were healthy (no women were pregnant or took oral contraceptives) regardless of the fact that, with regard to sex and age, they were found to have excessive hyperlipidaemia (see graph) (about 3% of all patients of the health centre) were sent to a special clinic at the Department of Medicine, Karolinska Hospital, where the analyses of serum lipids were repeated. If the values were found to remain high the patient was offered further examination, control, and treatment at this special clinic.

Age- and sex-matched controls with normal serum lipid values were selected from the same health centre.

At the clinic detailed history was taken according to a specially developed questionnaire. The physical examination was repeated—especially directed towards the finding of cardio-

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vascular, endocrine, renal, and liver disease, and stigmata of hyperlipidaemia. With regard to raised E.S.R. values, the patients were especially asked about recent infections. Laboratory tests comprised haemoglobin, W.B.C., E.S.R., serum transaminases (SGOT, SGPT), alkaline phosphatases, serum creatinine, protein-bound iodine in serum, serum paper electrophoresis, fibrinogen and urine analysis of protein and glucose. Altogether, 93 hyperlipidaemic and all control subjects were investigated with resting and exercise E.C.G. on a heart rate controlled bicycle ergometer (EMT 252 + EM 370, Elema, Sweden). The subjects exercised for six minutes on consecutive loads beginning with a heart rate of 90/min and increasing every sixth minute by 20 beats/min. An E.C.G. was recorded at each work load. The E.C.G. at rest and during exercise was interpreted by a clinical physiologist without knowledge of whether the E.C.G. was recorded from a control or hyperlipidaemic subject. Ischaemic S-T segment depressions were regarded as 4.1-4.4 according to the Minnesota code (1967).

Classification of the type of hyperlipidaemia followed the nomenclature of a recent W.H.O. report (Beaumont *et al.*, 1970).

For serum lipid determinations blood was allowed to clot at room temperature for one to two hours, serum was separated through centrifugation, frozen, and kept at -20°C until analysed. The lipid analyses were performed once weekly, using a semi-automatic autoanalyser technique for cholesterol (Block *et al.*, 1965) and for triglycerides (Kessler and Lederer, 1965). Serum phospholipids were analysed in a part of the present material by thin layer chromatography as recently described by Böttiger (1973 b). Serum lipoproteins were separated into very low, low, and high density lipoproteins in the preparative ultracentrifuge at densities of 1.006 and 1.063. The cholesterol and triglyceride content of these three lipoprotein families were then analysed.

Controls were investigated in the same way as the hyperlipidaemic patients.

Results

The original serum lipid values (cholesterol and triglycerides) causing referral to the special clinic are shown in the graph.

Original serum lipid values (triglycerides and cholesterol) in 101 persons incidentally found to be hyperlipidaemic. No persons with values below 300 mg/100 ml serum cholesterol and/or 2.0 mmol/l. serum triglycerides were included.

The distribution of the subjects according to the various types of hyperlipidaemia and of the normolipidaemic controls is given in table I. Thirty-two had a type II A pattern, 14 a type II B, 3 a type III, and 52 a type IV pattern. More females than males had a type II A pattern, while the opposite was true for type IV. The females were slightly older than the males. Age

TABLE I—Distribution of Subjects and Controls According to Type of Hyperlipidaemia (Beaumont *et al.*, 1970) (Mean $\pm$ S.E. of Mean)

Type	Total Cases	Men			Women		
		No.	%	Mean Age in Years	No.	%	Mean Age in Years
II A	32	8	22	48.6 $\pm$ 3.8	24	78	55.1 $\pm$ 1.6
II B	14	7	50	53.7 $\pm$ 3.0	7	50	54.2 $\pm$ 5.4
III	3	2			1		
IV	52	44	85	49.7 $\pm$ 1.4	8	15	50.6 $\pm$ 4.0
All	101	61	60	50.0 $\pm$ 1.2	40	40	54.0 $\pm$ 1.6
Controls	50	32	64	49.6 $\pm$ 1.8	18	36	56.0 $\pm$ 1.9

and sex distribution of the controls did not differ from the hyperlipidaemic group.

The E.S.R. values in the groups of hyperlipidaemic subjects and controls are given in table II. The significance of the differences between the values in individual groups of hyperlipidaemia is given in table III. Further, the values have been given for men and for women separately within the groups (table IV).

TABLE II—E.S.R. Values (Mean $\pm$ S.E. of Mean) in Different Types of Hyperlipidaemia

Type	No. of Cases	E.S.R. (mm/hr)	Percentage of individuals with E.S.R. $\geq$ 25 mm/hr
II A	32	24.3 $\pm$ 2.9	44
II B	14	29.4 $\pm$ 5.3	64
IV	52	14.9 $\pm$ 1.7	23
Normal controls	50	9.1 $\pm$ 1.2	6

TABLE III—Statistical Significance of the Differences in E.S.R. between Different Types of Hyperlipidaemia (*t* Test)

Type	<i>t</i> Test	P
II A—normals	5.62	<0.001
II B—normals	5.68	<0.001
IV—normals	2.78	<0.01
II A—Type IV	3.01	<0.01
II B—Type IV	3.48	<0.001
II A—Type II B	0.92	N.S.

N.S. = Not significant.

TABLE IV—E.S.R. values in Different Types of Hyperlipidaemia, Divided According to Sex (Mean $\pm$ S.E. of Mean)

Type	Men (mm/hr)	Women (mm/hr)	Difference (<i>t</i> Test)
II A	14.5 $\pm$ 3.4	27.9 $\pm$ 3.5	P < 0.05
II B	31.7 $\pm$ 8.8	26.7 $\pm$ 5.8	N.S.
IV	13.6 $\pm$ 1.8	21.9 $\pm$ 4.4	N.S.
Normals	9.1 $\pm$ 1.7	9.0 $\pm$ 1.8	N.S.

N.S. = Not significant

The E.S.R. was significantly higher in all types of hyperlipidaemia than in the controls. Persons with type II A and II B had higher E.S.R. values than those with type IV. For control subjects only 6% had E.S.R. values above 25 mm/hr in contrast to a figure of 64% for persons having a hyperlipidaemia of type II B. When subdivided according to sex, females having a type II A pattern had significantly higher mean E.S.R. than males with the same type of hyperlipidaemia.

Mean values for serum lipids were calculated in two groups, one with E.S.R. < 25 mm/hr and one with E.S.R. $\geq$ 25 mm/hr (table V). There was no significant difference in serum lipid values for subjects with "low" and "high" E.S.R. There was a tendency for the "high" E.S.R. group to be slightly older but this was not statistically significant in any of the three types.

TABLE V—Serum Lipid Values in Hyperlipidaemic Subjects with "Low" and "High" E.S.R. Respectively (Mean Value $\pm$ S.E. of Mean)

Type	No. of Cases	E.S.R. < 25 mm/hr			No. of Cases	E.S.R. $\geq$ 25 mm/hr		
		Cholesterol (mg/100 ml)	Triglycerides (mmol/l.)	Age in Years		Cholesterol (mg/100 ml)	Triglycerides (mmol/l.)	Age in Years
IIA	18	382 $\pm$ 10.7	1.63 $\pm$ 0.54	51.2 $\pm$ 2.7	14	408 $\pm$ 19.9	1.88 $\pm$ 0.59	57.3 $\pm$ 1.6
IIB	5	385 $\pm$ 15.5	3.00 $\pm$ 0.56	48.8 $\pm$ 6.8	9	362 $\pm$ 11.0	3.31 $\pm$ 0.86	53.5 $\pm$ 3.2
IV	40	286 $\pm$ 8.7	5.45 $\pm$ 3.73	50.0 $\pm$ 1.5	12	301 $\pm$ 13.9	4.95 $\pm$ 2.29	50.8 $\pm$ 3.2

TABLE VI—Mean Values for Serum Cholesterol, Triglycerides, Phospholipids, and Lysolecithin in Two Groups of Hyperlipidaemic Subjects with "Very Low" and "Very High" E.S.R. Respectively

Type	"Low" E.S.R. Group						"High" E.S.R. Group					
	No. of Cases	E.S.R. (mm/hr)	Cholesterol (mg/100 ml)	Triglycerides (mmol/l.)	Total Phospholipids* (μ g/ml)	Lysolecithin* (μ g/ml)	No. of Cases	E.S.R. (mm/hr)	Cholesterol (mg/100 ml)	Triglycerides (mmol/l.)	Total Phospholipids* (μ g/ml)	Lysolecithin* (μ g/ml)
IIA ..	7	8.7	403	1.65	150	12.1	7	38.4	413	1.82	163	11.8
IIB ..	4	6.4	384	3.13	181	14.2	4	39.5	378	2.94	173	11.7
IV ..	8	6.1	285	5.84	137	9.5	8	35.6	284	4.40	138	10.8

* Expressed as lipid phosphorous.

TABLE VII—End (Maximal) Work Load (W end) and End (Maximal) Heart Rate (HR end) (Mean $\pm$ S.E. of Mean) in Hyperlipidaemic Subjects Grouped into Two Ranges of E.S.R. and in Control Subjects

	Hyperlipidaemic Subjects						Control Subjects		
	E.S.R. < 25 mm/hr			E.S.R. $\geq$ 25 mm/hr			No. of Cases	W end	HR end
	No. of Cases	W end	HR end	No. of Cases	W end	HR end			
Males	36	1,063 $\pm$ 46	164 $\pm$ 3	17	790 $\pm$ 53	148 $\pm$ 4	32	1,196 $\pm$ 61	168 $\pm$ 3
Females ..	22	584 $\pm$ 30	153 $\pm$ 3	18	555 $\pm$ 56	148 $\pm$ 5	18	728 $\pm$ 59	161 $\pm$ 4
All	58	881 $\pm$ 45	160 $\pm$ 2	35	669 $\pm$ 40	148 $\pm$ 3	50	1,027 $\pm$ 55	166 $\pm$ 2

Two subgroups were selected on account of the E.S.R. values, one with "very low" and one with "very high" values. In these groups phospholipids were also analysed, the main purpose being to see if low levels of lysolecithin could offer an explanation to the high E.S.R. (table IV). The E.S.R. value in the "low" group was 6.8 mm/hr and in the "high" group close to 40 mm/hr in the three different types of hyperlipidaemia. There were no major differences in the concentrations of serum cholesterol, triglycerides, total phospholipids, or lysolecithin between the "low" and the "high" E.S.R. groups.

The findings on the exercise E.C.G. have been correlated to the E.S.R. values. The work loads and heart rates at the end of the exercise test—that is, usually after six minutes on maximal work load—are given in table VII and the significance of the differences between the groups in table VIII. From tables VII and VIII it can be summarized that work load and heart rate for both sexes tended to be—though not always significantly—higher in the control group than in the hyperlipidaemic group. Furthermore, in the hyperlipidaemic group patients with E.S.R. below 25 mm/hr, in particular males, had higher work loads and heart rates than those with E.S.R. above 25 mm/hr. It was thus thought justified to rely on the frequency of ischaemic S-T

TABLE VIII—Statistical Significance (P) of Differences in End Work Load (W end) and End Heart Rate (HR end) between Hyperlipidaemic Subjects with E.S.R. below and above 25 mm/hr. and Normolipidaemic Controls (C)

	E.S.R. < 25 — E.S.R. $\geq$ 25 mm/hr		E.S.R. < 25 mm/hr — C		E.S.R. $\geq$ 25 mm/hr — C	
	W end	HR end	W end	HR end	W end	HR end
Males ..	0.001	0.001	N.S.	N.S.	0.001	0.001
Females ..	N.S.	N.S.	0.05	N.S.	0.05	0.05
All ..	0.01	0.01	0.05	N.S.	0.001	0.001

N.S. = Not significant.

segment depressions at the highest work load as an estimate of differences in the frequency of myocardial ischaemia between the groups, as the main question was whether or not the group with high E.S.R. had more coronary artery disease than the other. The lower heart rate in this group would if anything lead to an underestimate of the frequency of ischaemic E.C.G. findings.

The frequencies of ischaemic S-T segment depressions (≥ 4.4) at maximal load are given in table IX. Among the hyper-

TABLE IX—Frequency (%) of Ischaemic S-T Segment depressions during Work (≥ 4.4) in Hyperlipidaemic Subjects and Controls Grouped into Two Ranges of E.S.R.

	Hyperlipidaemia									Controls			
	E.S.R. < 25 mm/hr				E.S.R. ≥ 25 mm/hr					No. of Cases	Percentage with S-T Depressions		
	No. of Cases	Percentage with S-T Depressions			No. of Cases	Percentage with S-T Depressions			P*				
		4·1-4·2	4·3-4·4	4·1-4·4		4·1-4·2	4·3-4·4	4·1-4·4					
Males ..	36	11	22	33	17	41	29	70	<0·001	32	3	10	13
Females ..	22	23	23	46	18	44	28	72	<0·001	18	11	6	17
All ..	58	16	22	38	35	43	29	72	<0·001	50	6	8	14

* Indicates significant differences between hyperlipidaemic subjects with E.S.R. $\geq$ 25 mm/hr and controls.

lipidaemic subjects with E.S.R. below 25 mm/hr 38% had ischaemic S-T segment depressions while the corresponding figure for hyperlipidaemic subjects with E.S.R. values above 25 mm/hr was 72%. In normolipidaemic controls the frequency of ischaemic S-T segment depressions was 13% for males and 17% for females. The frequencies in the controls differ significantly from the groups of hyperlipidaemic males and females with E.S.R. below 25 mm/hr on the 1% level and from the groups with E.S.R. above 25 mm/hr on the 0.1% level.

Discussion

In a prospective study on the development of myocardial infarction (Carlson and Böttiger, 1972) it was found that the E.S.R. also, at least for people above 60 years of age, appeared to be a "risk factor"—significantly more myocardial infarctions occurred in the group with initially raised E.S.R. than in those with normal E.S.R. values. Further studies on the same original patient material showed a positive correlation between E.S.R. values and the levels for serum cholesterol and triglycerides respectively (Böttiger, 1973 a).

In the present paper it is shown that also in persons with incidentally discovered *asymptomatic* hyperlipidaemia the E.S.R. values are higher than in normolipidaemic controls.

These observations raise two main possibilities: there is either a *direct* or an *indirect* relation between hyperlipidaemia and E.S.R.

If a *direct* relation existed, in which hyperlipidaemia would cause raised E.S.R., one would expect that the raised E.S.R. would be related to some specific lipoprotein, but since the E.S.R. values were higher in *all* types of hyperlipidaemia than in the control group this does not appear to be the case. Also one would expect to find quantitative differences in lipid levels between subjects with "normal" and with "raised" E.S.R. Analysis of serum lipid values in the individual groups of hyperlipidaemia in patients with "normal" and "raised" E.S.R. values (arbitrarily chosen limit value = 25 mm/hr) showed that there were no consistent and significant differences between the lipid values (tables V and VI). This clearly indicates that it is not the plasma levels of lipoproteins which per se causes an increase in the E.S.R. Though a statistical correlation between the E.S.R. and serum lipid values has been found (Böttiger, 1973 b), the serum lipoproteins were not responsible for the variation in E.S.R. in subjects with pronounced hyperlipidaemia.

The differences in E.S.R. values have been emphasized in two subgroups into which we allocated consecutive patients with "very low" and with "very high" E.S.R. values as matched pairs. Not even here were there any differences in lipid values between the two groups. In these selected groups we also determined the concentration of lysolecithin, which was found not to differ between the "high" and "low" E.S.R. groups. Several lines of evidence suggest that lysolecithin by its surface active properties might decrease the E.S.R., conversely a low level might enhance the E.S.R. Since lysolecithin in blood at least partly is derived from the enzyme lecithin-cholesterol-acyltransferase and the enzyme deficiency is associated with hyperlipidaemia, it was of interest to see if high E.S.R. in hyperlipidaemia was related to low lysolecithin. Our data are not in favour of such a hypothesis.

There are no data speaking in favour that high E.S.R. would in itself cause hyperlipidaemia. On the contrary in most situations with high E.S.R. such as acute infections, acute myocardial infarctions, and malignancies, serum lipid levels decrease.

Several possibilities exist with regard to an *indirect* relation between E.S.R. and serum lipids.

One disorder that might cause both high lipid levels and

raised E.S.R. is autoimmune thyroiditis. A hypothyroidism induced by autoimmune mechanisms would lead to raised serum lipids and E.S.R. Larson (1962) found a negative correlation between the E.S.R. and values for protein-bound iodine in hypothyroidism. Three cases where hyperlipidaemia was attributed to hypothyroidism have been excluded from this material. Otherwise neither the clinical nor the laboratory investigations showed any signs of hypothyroidism in our hyperlipidaemic subjects.

Another possibility is disorders interfering with the serum protein pattern such as liver and renal diseases. Hyperlipidaemia is a rare manifestation of multiple myeloma (*British Medical Journal*, 1972). This disorder may be associated with so called autoimmune hyperlipidaemia, which also may exist alone (Beaumont, 1970) and which is caused by blockade of lipolysis induced by antilipoprotein antibodies or antienzyme antibodies, a disease process that could also result in raised E.S.R. But obviously these indirect relations most often are encountered in the presence of overt disease of some kind, which our patients did not show as they were asymptomatic and subjectively healthy.

Finally, could the hyperlipidaemia cause silent disease leading to raised E.S.R.?

The findings of a higher frequency of pathological E.C.G.s in the group of hyperlipidaemic subjects with E.S.R. above 25 mm/hr than in those below 25 mm/hr raise two possibilities. (1) High E.S.R. is in itself a "pathogenic risk factor" for ischaemic heart disease. Such a relation could explain the high incidence of ischaemic E.C.G.s in the group with high E.S.R. It could also fit with the observation that E.S.R. is a risk factor for ischaemic heart disease. However, it could not explain the high incidence of raised E.S.R. in subjects *selected on account of asymptomatic hyperlipidaemia*. (2) The hyperlipidaemia causes silent vascular disease of which ischaemic S-T segment depressions during exercise are one expression. This disease causes a raised E.S.R., but need not necessarily yet give rise to ischaemia or myocardial damage as the raised E.S.R. in this context is only an indication of pathological processes in the vessels. In fact the S-T segment depressions observed do not imply myocardial damage but rather diseased coronary vessels. The subjects were asymptomatic regarding myocardial involvement (angina) even during maximal work load. Thus it seems reasonable for the time being to conclude that the raised E.S.R. found in hyperlipidaemic subjects is caused more by hidden vascular disease than directly by serum lipid levels. The indirect relation between hyperlipidaemia and E.S.R. may in part be explained as follows. Hyperlipidaemia causes vascular disease (atherosclerosis) which may result in raised E.S.R. Such a relation may also explain why raised E.S.R. has been found to be a so-called "risk factor" for ischaemic heart disease. Further studies on this problem, including plasma protein analysis, are under way.

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