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HYPERLIPEMIA AND HYPERLIPOPROTEINEMIA /HLP/ SCREENING AMONG THE CHILDREN FROM PREMATURE MYOCARDIAL INFARCTION RISK FAMILIES

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Serum lipids and lipoproteins were investigated in the premature myocardial infarction (PMI) risk families before 45 years of age with the aid of screening for hyperlipemia and hyperlipoproteinemia (HLP): in the case of 174 persons from Csongrád County from the Departments of Internal Medicine I and II and of 42 patients (fathers) suffering from PMI and their 79 "high risk" children from Heves County.

In the investigated three groups of "high risk" children the genetically determined antiatherogenic HDL-Ch level diminished in 34.8, 52.3, 40.5 per cent.

Significant negative correlation was detected between the serum HDL-Ch and beta-lipoprotein; significant positive correlations were found between the HDL-Ch and the serum lipase activity; between the beta-lipoprotein and the phospholipid level; significant negative correlation was proved between the HDL-Ch and the phospholipid level in the group of PMI patients and their offsprings. The Ch/Tg, and the HDL-Ch ratios were significantly diminished in the PMI patients' group against the risk children' group, while the Ch/HDL-Ch rate was significantly elevated.

INTRODUCTION

Plasma lipoproteins and apolipoproteins are subjects of interest because of their association with coronary artery disease. Elevations of total and low-density lipoprotein (LDL) cholesterol and the main apolipoprotein constituent of LDL, apolipoprotein B, are associated with an increased risk of

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coronary artery disease. Similarly, elevated plasma levels of Lp/a/ are seen more frequently in patients with premature coronary artery disease. Conversely, low levels of high-density lipoprotein (HDL) cholesterol and its major protein constituent, apolipoprotein A-I, are also associated with an increased risk of coronary artery disease /4b, 12a/.

Regression analyses were performed by Rosenbaum et al /26b/ with the value of the cardiovascular risk factor variable for the child as the dependent variable and race, sex of child and either mother's values, father's values, or both mothers's and father's values as the independent variables. The most significant relationship between parents and their children was for height; parental serum lipids and lipoprotein tended to increase with the child's age. Child-father regression coefficients and child-mother regression coefficients were generally significant after age of 2 years for total cholesterol. Less association was noted for triglycerides and lipoproteins. Parental diastolic blood pressure was a poor predictor of children's values; the regression coefficients for systolic blood pressure were higher and more significant /26/b/.

Serum lipid and lipoprotein levels at the age of 7 years were associated with previously measured levels as early as 6 months of age and infants with unfavourable levels were likely to have similar adverse levels at 7 years of age. In addition, increases in obesity between 6 months and 7 years of age were positively associated with increases in levels of serum triglycerides /5/a/.

As generally known the hyperbeta-lipoproteinemia (HBlp) and hypertriglyceridemia (HTg) are risk factors for premature myocardial infarction (PMI) /28, 3, 14, 19/. High density lipoprotein-cholesterol (HDL-Ch), low density lipoprotein-Ch (LDL-Ch) and the very low density lipoprotein-Ch (VLDL-Ch) proved to be genetically determined /20, 26/ among the risk factors.

Heinle et al /8/ found 25 per cent HLP type IV and 29 per cent HLP type II among their coronary sclerotic patients. Pados et al /23/ detected different types of HLP of the men's and

women's group - 59.3 per cent and 40.7 per cent resp. - suffering from PMI. HLP type IV or HLP type IIb and IIa were found to be the most frequent ones in the myocardial infarct patient's group /12/. According to the data of Szabó et al. /30/ HLP was 61.3 per cent among the infarct patients and 30.9 per cent in their offsprings.
It seemed to be useful to investigate the serum lipid and lipoprotein parameters in families at high risk for PMI.

MATERIALS AND METHODS

73 persons, 26 PMI patients and 47 "high risk children" 1.5-17.5 years from 26 families of the I. and II. Department of Medicine, Medical University of Szeged, 101 persons 24 PMI patients and 77 "high risk children" from 44 families of the Department of Internal Medicine, Hospital of Szeged and 121 persons 42 PMI patients and 79 offsprings from 42 families from the County Heves with high risk of PMI (under 45 years) were investigated for serum lipids [total Ch, Tg, phospholipid (=Phl)] and for lipoproteins (HDL-Ch), beta-lipoprotein (=Blp) and for lipase activity.
Serum cholesterol (Ch) and triglycerides (Tg) were measured by Goedecke-UV test, enzaChol-F (Goedecke), (EnzGlycid GPO) Goedecke.
The antiatherogenic HDL-Ch was measured after precipitation with Na-phosphowolframat and $MgCl_2$, the phospholipide (Phl) was determined fluorimetrically (1,6-Diphenyl-1,3,5-hexatriene (SIGMA), the serum lipase activity was measured by Boehringer-Lipase test (No 262358, No 263346 Lipase Monotest 10). The distribution of the hyperlipoproteinemias (HLP) types was given. The linear correlations between the serum lipids and lipoproteins were estimated in the patient-group originating from County Heves.

RESULTS

In the first group among the 26 PMI patients there was 15.3 per cent HLP II.a type (Ch > 6.5 mmol/l,hyperbeta-lipoproteinemia = NBLP = beta - lipoprotein > 8.5 g/l), 15.3 per cent HLP type II.b (HCh + HTg/Tg > 2.5 mmol/l), 3.8 per cent HLP type IV. in 31.8 per cent the HDL-Ch level diminished

under 1.2 mmol/l. The HDL-Ch diminished in 34.8 per cent in the high risk children's group (n = 47), hyperbeta-lipoproteinemia was 4.3 per cent, HLP type IV. was the same per cent.
Ch/Tg ratio elevated over 8 in 30.6 per cent of patients in 57.8 per cent of them this ratio was informative for hypercholesterolemia. In the 17.7 per cent of the investigated families the total Ch/HDL-Ch rate was elevated (> 7.0), in all of them with 100 per cent informative for hypercholesterolemia.

In the second group 101 persons from 44 families were investigated for lipid risk factors. Among the PMI (n = 24) there were 20.8 per cent HLP type IIb, 16.6 per cent HLP type IV and 8.3 per cent HLP type IIa, 20.8 per cent hypercholesterolemia without hyper -beta-lipoproteinemia, 4.2 per cent HTg, 8.3 per cent HBlp. The antiatherogenic HDL-Ch diminished in 25 per cent of cases.

In the high risk offsprings' group (n = 77) the HDL-Ch was diminished in 52.3 per cent (< 0.85 mmol/l under 14 years and < 1.1 mmol/l over 14 years), 2.6 per cent HCh /2/77/, 6.5 per cent /5/77/ HTg, 5.2 per cent /4/77/ HBlp, 1.3 per cent /1/77/ HLP IIb, and there were no HLP type IIa and type IV (Table Ia) cases.

In the third group (County Heves) the mean values of the serum lipids, of the lipoproteins, the Ch/HDL-Ch ratio were in the normal range, while the HDL-Ch was under 1.5 mmol/l (Table I) in the high risk offspings' group. Lipase activity was low in 14.9 per cent (20-40 U/l). The Phl level was more than 3 mmol/l in 25.3 per cent /22/87/.

The PMI patients proved to be HCh, HTg, HBlp, and hypoHDL-Cholesterolemic ones according to the mean values (Table I).

In the PMI group the frequency of HLP type IIa was 38.1 per cent /16/42/, the same as HLP type IIb, HLP type IV was only 4.8 per cent /2/42/, HCh was 14.3 per cent /6/42/ without HBlp, HDL-Ch diminished in 42.0 per cent.

In the high risk offsprings' group there was 3.8 per cent /3/79/ HLP type IIa, 2.5 per cent /2/79/ HLP type IIb, 3.8 per cent HCh without HBlp, 6.3 per cent /5/79/ HBlp. The antiatherogenic HDL-Ch diminished under 1.2 mmol/l in 40.5 per cent /32/79/ (Table Ia).

TABLE I

Serum lipid and lipoprotein values in premature myocardial infarct patients (County Heves)

	Cholesterol mmol/l	Triglycerid mmol/l	HDL-Ch mmol/l	Beta-lipoprotein g/l	Lipase E/l	Phospholipid mmol/l
n = 42						
$\bar{X}$ =	6.71	2.6	1.2	9.39	65.6	3.86
S.D.$\pm$	1.59	2.46	0.45	4.39	22.0	1.71
			High risk children			
n = 79						
$\bar{X}$ =	4.85	0.95	1.35	5.41	52.5	2.43
S.D.$\pm$	0.82	0.49	0.32	2.41	25.4	0.44

TABLE I.a

Percentual incidency of the hyperlipemia and hyperlipoproteinemia in the high risk premature myocardial infarct families

	HCh	HLP II.a	II.b	IV.	HBlp	decreased HDL-Ch	%
1. group (I.and II. Department of Internal Medicine, Med.Univ.Szeged)							
PMI patients (n = 26)	0	15.3	15.3	3.8	0	31.8	
High risk children (n = 47)	0	0	0	4.3	4.3	34.8	
2. group (Dept. of Internal Medicine, County Hospital, Szeged)							
PMI patients (n = 24)	20.8	8.3	20.8	16.6	8.3	25.0	
High risk children (n = 77)	2.6	0	1.3	0	5.2	52.3	
3. group (County Heves)							
PMI patients (n = 42)	14.3	38.1	38.1	4.8	0	42.0	
High risk children (n = 79)	3.8	3.8	2.5	0	6.3	40.5	

HCh = hypercholesterolemia without HLP
HBlp = hyperbeta-lipoproteinemia without HLP

TABLE I.b

Lipid and lipoprotein atherogenic ratios

Groups		Ch/Tg	Ch/HDL-Ch	HDL-Ch/Ch
I.	PMI	23	14	14
	$\bar{X}$ =	4.01	4.43	0.24
	S.D.±	3.03	1.38	0.07
	p	= 0.057	> 0.05	> 0.05
	Risk children	35	31	31
	$\bar{X}$ =	5.31	3.86	0.28
	S.D.±	2.12	1.30	0.08
II.	PMI	21	19	19
	$\bar{X}$ =	3.83	7.97	0.13
	S.D.±	2.19	2.35	0.04
	p	< 0.001	< 0.001	< 0.001
	Risk children	79	73	73
	$\bar{X}$ =	5.02	5.37	0.20
	S.D.±	2.26	1.80	0.07
III.	PMI	38	38	38
	$\bar{X}$ =	4.15	5.92	0.19
	S.D.±	2.51	2.70	0.06
	p	< 0.05	< 0.001	< 0.001
	Risk children	68	68	68
	$\bar{X}$ =	6.03	6.67	0.29
	S.D.±	2.82	1.06	0.07
Controls	n =			17
3 - 6 year	$\bar{X}$ =			0.19
	S.D.±			0.04
6 -10 year	n =			14
	$\bar{X}$ =			0.187
	S.D.±			0.04
10-14 year	n =			18
	$\bar{X}$ =			0.2
	S.D.±			0.05

Significant positive linear correlation was proven between the serum Ch and Tg, Ch and BLp, Ch and Phl, significant negative correlation was proven between the HDL-Ch and Blp, between the Phl and HDL-Ch in the investigated third group. There was a positive correlation between the HDL-Ch and lipase activity, between the Blp and Phl in the total group (PMI patient and their high risk children) (Table II).

There was no correlation between the Blp and Ch, and between the HDL-Ch and the lipase activity in the group of PMI patients (Table III).

The correlations between the Ch and Tg, HDL-Ch and lipase activity, HDL-Ch and Phl were absent in the high risk offsprings' group (Table III). The lipid and lipoprotein atherogenic rations are seen in the Table I.b according to the different groups. The Ch/Tg, Ch/HDL-Ch and the HDL-Ch (Ch ratios significantly changed in the II. and III.groups; the Ch/Tg and the HDL-Ch/Ch ratios were signicantly diminished in the PMI patients' group against the high risk children's group, while the Ch/HDL-Ch rate was significantly elevated. These correlations did not change significantly in the cases of the first group.

DISCUSSION

Andersen et al /1/ found among 1407 Danish children whose fathers have died from ischemic heart disease before age of 45, 15 per cent HCh 8 per cent HTg, 1.8 per cent familial HLP.

Glueck et al /6/ among 233 children of 70 parents with a myocardial infarction before age of 50 years found 2.5 per cent with HCh. Blumenthal et al /4/ found 13.8 per cent with HCh, Hennekens et al /10/ found 16.1 per cent high risk children with elevated serum Ch. Rissanen and Nikkilä /25/ among 213 children of 104 men with angina pectoris before age of 56 years found hyperlipemia in around 23 per cent as opposed to 13 per cent in the control group.

TABLE II

Linear correlation coefficients between the serum lipids and lipoproteins (high risk families, premature infarct patients /parents/ and their children)

n=83 (29+54)	Cholesterol r	Triglycerid r	HDL-Ch r	Beta-lipoprot. r	Lipase r	Phospholipid r
Cholesterol	1.00	0.55^{x}	-0.10	0.53^{x}	0.15	0.61^{x}
Triglycerid	0.55^{x}	1.00	-0.40^{x}	0.68^{x}	0.06	0.81^{x}
HDL-Ch	-0.10	-0.40^{x}	1.00	-0.44^{x}	0.25	-0.30^{x}
Beta-lipoprotein	0.52^{x}	0.68^{x}	-0.44^{x}	1.00	0.11	0.75^{x}
Lipase	0.15	0.06	-0.24^{x}	0.11	1.00	0.07
Phospholipid	0.61^{x}	0.81^{x}	-0.30^{x}	0.75^{x}	0.07	1.00

^{x} $p < 0.05$

TABLE III

Linear correlation coefficients between the serum lipids and lipoproteins (premature myocardial infarct patients)

n = 29	Cholesterol r	Triglycerid r	HDL-Ch r	Beta-lipoprot. r	Lipase r	Phospholipid r
Cholesterol	1.00	0.48^{x}	-0.09	0.32	-0.10	0.39^{x}
Triglycerid	0.48^{x}	1.00	-0.52^{x}	0.66^{x}	-0.03	0.78^{x}
HDL-Ch	-0.09	-0.52^{x}	1.00	-0.57^{x}	-0.27	-0.44^{x}
Beta-lipoprotein	0.33	0.66^{x}	-0.57^{x}	1.00	-0.06	0.72^{x}
Lipase	-0.09	-0.04	-0.27	-0.06	1.00	-0.14
Phospholipid	0.39^{x}	0.78^{x}	-0.44^{x}	0.72^{x}	-0.14	1.00
Linear correlation coefficients between the serum lipids and lipoproteins (children with high risk)						
n = 54						
Cholesterol	1.00	0.13	0.14	0.33^{x}	0.06	0.61^{x}
Triglycerid	0.13	1.00	-0.29^{x}	0.66^{x}	-0.17	0.65^{x}
HDL-Ch	0.14	-0.29^{x}	1.00	-0.28^{x}	-0.18	0.02
Beta-lipoprotein	0.33^{x}	0.66^{x}	-0.28^{x}	1.00	0.00	0.67^{x}
Lipase	0.06	-0.17	-0.18	0.00	1.00	-0.08
Phospholipid	0.61^{x}	0.65^{x}	0.02	0.67^{x}	-0.08	1.00

^{x} $p < 0.05$

In the literature there are data about the negative correlation between the HDL-Ch value and the severity of the myocardial infarction, and positive correlation between the LDL-Ch level /8/. Apolipoprotein A-I (Apo-A-I) proved to be a marker for coronaria-sclerosis /18/. Apo-A-I is an important functional part of the HDL-Ch. The LDL-Ch was significantly diminished, the HDL-Ch significantly elevated in the physically trained group /2/; by the elevation of the activity of lipoprotein lipase in muscles and in the fat tissue.

Franzen and Fex /5/ showed a positive correlation between the Tg level and Apo-A-I/HDL-Ch ratios; a negative correlation between the HDL-Ch and Tg. There was a strong correlation between the HDL-Cl level of the high risk sons and their fathers suffering from PMI.

Lees and Lees /16/ published significantly less Apo-A-I value than in the control group in the first degree relatives of PMI patients and significantly higher Apo-B values. In our own material the total Ch/HDL-Ch ratio was 100 per cent informative for HLP and HCh, while the Ch/Tg ratio was false positive in 42.4 per cent, originating from the low Tg levels with normal Ch values. We have detected compensatoric HDL-Ch elevation in 28.5 per cent of the PMI patients. Apo-B value proved to be the best discriminative factor between the male family members and Apo-A-I between the female family members and the control group /13/.

Oberhänslie et al /20/ found the HDL/serum Ch and HDL/LDL/Ch ratio to be useful as the indicator for PMI. Heldenberg et al /9/ published elevated Ch and HDL-Ch levels in the high risk children of PMI fathers.

Goldstein et al /7/ detected 60 per cent primary HLP, Ibsen /11/ detected more frequently familial HLP in the high risk family members. In Somogyi's /29/ material there was 24.3 per cent HLP type IIa in the high risk children's group, 60.3 per cent HLP in the PMI patients' group and 31 per cent HLP in their offsprings.

Longitudinal assessment of children with elevated lipid and lipoprotein levels may permit early identification of risk factors which increase the risk to coronary heart disease in

adulthood (Ch, Tg, LDL-Ch) or decrease it (HDL-Ch) /15/.

To establish the value of screening children for hypercholesterolemia predicting adult-age risk for the same condition /21/ stated that cholesterol screening in childhood proved to be predictive for adult HCh.

Familial hypercholesterolemia is based on the structural mutation in the LDL-receptor gene, which is one among the most common inborn errors of metabolism /24/.

Romics et al /27/ observed significantly elevated Ch, Tg, LDL and VLDL-Ch, diminished HDL-Ch, VLDL-LDL ratio in the group of PMI persons.

We found 72.5 per cent hyperlipemia or HLP in PMI patients, the antiatherogenic HDL-Ch was under 1.2 mmol/l value in 52.3 per cent of the 77 high risk children from 44 PMI families.
Decreased plasma HDL-Ch and Apo-A-I levels have been associated with premature coronary disease (PCAD). Ordovas et al /22/ detected Apo-A-I gene polymorphism associated with PCAD and familial hypo-alpha-lipoproteinemia.
In our third investigated group from County Heves the antiatherogenic HDL-Ch level diminished in 42.0 per cent of the PMI patients and in 40.5 per cent of their descendants. The Ch/Tg and the HDL-Ch/Ch ratios were significantly diminished in the PMI patients' group against the high risk children's group, while the Ch/HDL-Ch rate was significantly elevated in our own first and second groups investigated.

Szamosi et al /30/ and Czinner et al /4a/ screening the Hungarian high risk families for arteriosclerosis have got significantly higher Ch and lower HDL-Ch levels among the risk children of PMI patients.
According to literature data and our own results the screening for lipid and lipoprotein parameters among the children of high risk families seems to be useful inspite of the poor preventive and therapeutic possibilities. Rational diet and sufficient physical activities could be more advisable as any drugs in this early age.

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