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PLASMA LIPID AND LIPOPROTEIN LEVELS IN RHEUMATIC FEVER*

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Among childhood cardiac disorders, acute rheumatic fever and rheumatic heart disease still maintain their importance as far as morbidity and mortality are considered. Despite the fact that the etiology of rheumatic fever related to streptococcus, and its multisystem manifestations are well-defined, its pathogenesis is still vague, even today.

The role of lipids was first mentioned in the literature by Coburn[1,2] in 1943, who claimed that high-cholesterol diets increased the body's resistance to rheumatic fever and that phospholipids may be involved in the etiology of rheumatic fever. Some data support this view. For example, following skin infections, the antistreptolysin-0 (ASO) response is low when compared with streptococcal tonsilitis. Rheumatic fever never occurs following skin infections. This may be due to the possible preventive effect of lipids under the layers of the skin[3]. It is also known that the toxic effect of streptolysin on myocardial cells increases in low plasma cholesterol and high-density lipoprotein levels (HDL-C)[4]. In some inflammatory diseases, rheumatoid arthritis in particular, the drop in the serum cholesterol level is a common clinical finding[5].

However, levels of serum lipids and lipid fractions are still questions which need to be investigated in rheumatic patients. Does the low lipid level in the rheumatic cardiac patient play a role of host factor or does inflammation cause a biochemical change by increasing catabolism? In this study, aimed at finding answers to the above questions, we compared the serum total lipid, cholesterol, high density

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lipoprotein (HDL-C) and low density lipoprotein (LDL-C) levels, as well as th HDL-C/LDL-C, and HDL-C/triglyceride ratios of the patients diagnosed as havir rheumatic fever with the patients with uncomplicated upper respiratory tra streptococcal infections (USI) and those of the normal controls.

Material and Methods

This study was carried out on 25 patients suffering from rheumatic fever, 20 with uncomplicated upper respiratory tract streptococcal infections and 50 follow-up patients, who had been admitted to the Pediatric Cardiology Unit of Gazi University Medical Faculty.

Of 25 rheumatic fever cases, 13 displayed signs of active rheumatic carditis, and 12 had complaints of pure acute rheumatic arthritis (ARA). The diagnoses of these patients were made by referring to the Modified Jones criteria[6]. Group A beta hemolytic streptococci were cultivated in the throat cultures of the patients with uncomplicated streptococcal infections. Four weeks after the first examination this group was again checked for rheumatic fever complications.

Five cc blood samples were taken from the upper arm veins of the patients following a 12-hour fasting period. These samples were kept at normal room temperatures for two hours. The serums which were extracted by centrifugation for ten minutes at 3000 rpm were kept an additional five days at 4°C for analyses.

In a total of 95 sera, the total lipid and total cholesterol levels were measured by the Phospho-vanillin and Loffler Methods, respectively[7,8]. To determine the HDL-C and triglyceride rates, the Sigma Chemical Company's Kit No. 350, and Triglyceride No. 405 kits were used. As for the LDL-C rates, they were calculated by using the total cholesterol values.

Other factors, which could interfere with the lipid values were eliminated in all cases by systematic physical examinations and by evaluating the blood sugar, liver function tests, CBC and urinalysis. Special attention was given to the selection of patients. Those who had not been subjected to drug administration prior to admission to our hospital, and those with rheumatic fever complaints who had experienced their first rheumatismal attacks were included in the present study.

After the samples were taken, the patients in the carditis group were given prednisolone (2 mg/kg), those in the arthritis group salicylates (100 mg/kg) and both groups were treated with benzathine penicillin-G. Four weeks later, second samples were taken from the active carditis patients.

The Student's *t* test and correlation coefficient calculations were used for statistical analysis.

Results

The distribution of cases according to age and sex, total lipid, total cholesterol, HDL-C, triglyceride, LDL-C, cholesterol/HDL-C and HDL-C/triglyceride rates are listed in Tables I and II.

TABLE I: Distribution of Cases According to Age and Sex

Groups	5-9 Years Male	5-9 Years Female	10-15 Years Male	10-15 Years Female	Total
Active Carditis	2	–	3	8	13
ARA	4	–	6	2	12
USI	4	12	1	3	20
Control	26	23	22	24	95

USI : Uncomplicated upper respiratory tract streptococcal infection.
ARA : Acute rheumatic arthritis.

TABLE II: Mean Values of Serum Lipids and Lipoprotein Fractions in Rheumatic and Non-Rheumatic Patients*

Measured Fractions (mg/dl)	GROUPS Active Carditis n: 13	ARA n: 12	USI n: 20	Control Group n: 50
Total lipids	546.77 ± 27.35*	496.92 ± 30.12	508.8 ± 23.06	523.56 ± 15.90
Total Cholesterol	135.08 ± 7.45	150.17 ± 12.54	149.1 ± 9.21	158.78 ± 5.03
HDL-C	25.23 ± 2.55	30.67 ± 2.35	30.7 ± 2.90	31.24 ± 1.38
Triglyceride	136.15 ± 11.25	113.50 ± 10.36	95.5 ± 7.71	104.96 ± 5.13
LDL-C	83.38 ± 6.88	86.00 ± 10.97	99.3 ± 7.19	106.55 ± 4.93
Cholesterol / HDL-C ratio	6.01 ± 0.65	5.10 ± 0.80	5.83 ± 0.64	5.60 ± 0.32
HDL-C / Triglyceride ratio	0.20 ± 0.02	0.30 ± 0.03	0.39 ± 0.06	0.33 ± 0.02

* Mean ± $S_{\bar{x}}$

In the comparison between the control group and the group with active carditis, it was established that total cholesterol, HDL-C, and LDL-C/triglyceride average levels were lower in the latter, while the average triglyceride levels were higher

than the former, thus presenting an important difference between the two groups (Table III). The discrepancy encountered between the average values of all parameters of the control group with acute rheumatic arthritis was not considered statistically important.

TABLE III: Comparison of Mean Values of Active Carditis and Control Group

Measured Fractions (mg/dl)	Control Group ($\bar{X} \pm S\bar{X}$)	Active Carditis ($\bar{X} \pm S\bar{X}$)	t	p
Total Lipids	523.56 ± 15.90	546.77 ± 27.35	0.73	> 0.05
Total Cholesterol	158.78 ± 5.03	135.08 ± 7.45	2.64	< 0.05
HDL-C	31.24 ± 1.38	25.23 ± 2.55	2.07	< 0.05
Triglyceride	104.96 ± 5.13	136.15 ± 11.25	2.39	< 0.05
LDL-C	106.55 ± 4.93	83.38 ± 6.88	2.74	< 0.05
Cholesterol / HDL-C	5.60 ± 0.32	6.01 ± 0.65	0.03	> 0.05
HDL-C / Triglyceride	0.33 ± 0.02	0.20 ± 0.20	3.25	> 0.05

No significant difference was observed between the groups of patients with upper respiratory tract streptococcal infections and the patients with acute rheumatic arthritis. In the comparison between the group of patients with upper respiratory tract streptococcal infections and the group with active rheumatic carditis, the average triglyceride values were found to be higher and the rate of HDL-C/triglyceride lower in the latter than the former, a finding, which was found statistically significant (Table IV).

Similarly, in the comparison between the groups of patients with acute rheumatic arthritis, and the group with active rheumatic carditis, it was established that the HDL-C/triglyceride levels in the latter were significantly lower than the levels of the former. The difference in other parameters was considered to be insignificant (Table IV).

In all the groups, a negative correlation between the HDL-C levels and the erythrocyte sedimentation rate was observed ($r = -0.548$, $p<0.05$).

It was seen in the following visits of the active carditis patients two and four weeks after, that as the activity decreased, the low levels of HDL-C increased, reaching the normal control levels.

TABLE IV: Statistical Comparison of Mean Values of USI, ARA and Active Carditis Groups*

Measured Fractions (mg/dl)		$\bar{X} \pm S\bar{X}$	t	p
Total Lipids	USI	503.00 ± 23.06	1.06	> 0.05
	Carditis	546.77 ± 27.35	1.23	> 0.05
	ARA	436.92 ± 30.12		
Total Cholesterol	USI	149.10 ± 9.21	1.37	> 0.05
	Carditis	135.08 ± 7.45	1.04	> 0.05
	ARA	150.17 ± 12.54		
HDL-C	USI	30.70 ± 2.30	1.42	> 0.05
	Carditis	25.23 ± 2.55	0.67	> 0.05
	ARA	30.67 ± 2.35		
Triglyceride	USI	95.50 ± 7.71	2.98	< 0.05
	Carditis	136.15 ± 11.25	1.48	> 0.05
	ARA	113.50 ± 10.36		
LDL-C	USI	99.30 ± 7.19	1.60	> 0.05
	Carditis	83.38 ± 6.88	0.20	> 0.05
	ARA	86.00 ± 10.97		
Cholesterol / HDL-C	USI	5.83 ± 0.64	0.31	> 0.05
	Carditis	6.01 ± 0.65	0.43	> 0.05
	ARA	5.10 ± 0.80		
HDL-C / Triglyceride	USI	0.39 ± 0.06	2.71	< 0.05
	Carditis	0.20 ± 0.02	2.50	< 0.05
	ARA	0.30 ± 0.03		

* Mean values of all parameters of USI and ARA patients were found to be insignificant when compared with the control group.

USI : Uncomplicated upper respiratory tract streptococcal infection.

ARA : Acute Rheumatic Arthritis.

Discussion

Researchers investigating the pathogenesis of rheumatic fever have reported that this disorder occurs only after upper respiratory tract streptococcal infections and that it is not encountered in children after first having a streptococcal impetigo[7,8].

Similarly, it has been observed that the antistreptolysin-0 (ASO) titers were low in children suffering from streptococcal impetigo[9-11]. Furthermore it appears to be

impossible to explain this finding associated only with rheumatogenic-nephritogenic types of streptococci[9,11,12]. Since rather low levels of ASO response following cutaneous infections can neither be connected to the immunogenic unresponsiveness of the host, nor to the insufficient streptolysin-0 secretion of the type causing cutaneous infection, other local or systemic factors affecting the ASO response of the host should be taken into consideration.

It was demonstrated that the biological activity of streptolysin-O is inhibited by cholesterol[9]. As is known, cholesterol is one of the most important components of cutaneous lipids, especially in children[13]. A number of researchers in their studies displayed that skin lipids inhibit both the toxic and antigenic effects of streptolysin-O[3,12,14,15]. In addition, rheumatic fever has not been observed in patients with high cholesterol levels due to hypothyroidism, nephrosis and diabetes[16]. Although it has been established that the streptolysin-O inhibitory characteristics of rabbits, fed with cholesterol-rich diets, increased when their serum cholesterol had reached four or five times higher levels than the normal[17], the same result was not observed in the human sera. It is claimed, that the reason for this development is that the major portion of cholesterol in the human serum is in the form of an ester linked with lipoproteins, and that the free cholesterol level in humans was essentially low[12,17,18].

In our study, the cholesterol levels in the group suffering from active rheumatismal carditis were found to be significantly lower than those of the control group. This finding corroborates with previous studies asserting that the tendency in hypocholesterolemic patients for rheumatic fever is greater[14], and other studies claiming that cholesterol could prevent the occurrence of rheumatic fever by inhibiting streptolysin-O[12,17,19]. The low level of HDL-C in active rheumatic carditis cases confirms the studies asserting that lipoproteins possess streptolysin-O inhibiting characteristics[18,20,21], and also the positive correlation between levels of HDL-C and the sedimentation rate suggests a relation between this finding and the hypercatabolism in inflammatory diseases, as in rheumatoid arthritis[5]. It is an established fact that after reaching specific levels, streptolysin-O accumulates in body tissues and cells, and that it displays its effect by attaching itself to the 3-b-OH tips of cholesterol molecules present in the lipoprotein membrane of the cells[15,19,22]. It can be said that the cholesterol molecules fed by streptolysin-O on the membrane of the myocardial cells in patients suffering from active carditis most probably are not sufficiently eliminated by HDL or that the streptolysin-O can reach toxic levels easily when the number of HDL molecules in coping with streptolysin-O is inadequate.

In fact, it has been demonstrated that corticosteroids administered in rheumatic carditis cases has an increasing effect on the alpha and beta lipoprotein levels[23,24]. Therefore, one can consider that this effect might play a role in carditis cases administered corticosteriods by inducing early remissions.

Despite the fact that the direct toxic effect of streptolysin-O on myocardial tissue has been proven through experimental studies, an animal model has not been developed yet. Similarly, the inhibition of streptolysin-O by cholesterol was established through direct laboratory methods, but this finding has not been demonstrated in experiments of hypercholesterolemic human serums. Therefore, the subject is still open for investigation.

Consequently. the findings we achieved in this study demonstrated that triglyceride levels in rheumatic active carditis cases were high, and total cholesterol, HDL-C levels, and HDL-C/triglyceride rates were evidently low. The level of HDL-C, which is known for its protective effect on the heart, is the result of increased catabolism caused by inflammation rather than a host factor involved in the development of the disease. However, the low levels of HDL-C still seem to be a rick factor in rheumatic carditis.

Summary

This study was conducted to clarify the role of plasma lipid and lipoprotein fractions in the pathogenesis of acute rheumatic fever. Plasma lipid and lipoprotein patterns were determined in a total of 95 subjects consisting of 25 acute rheumatic fever (13 active carditis and 12 acute arthritis), 20 uncomplicated upper respiratory tract streptococcal infections (USI) and 50 healthy controls. The mean total cholesterol, HDL-C levels and HDL-C/triglyceride ratio were found to be low and the triglyceride level was found to be high in the active carditis groups when compared with the ARA, USI and control subjects. A negative correlation between the HDL-C level and the erythrocyte sedimentation rate was found in the active cases. These findings seem to be the result of increased catabolism in active carditis patients rather than a host factor involved in the development of the disease.

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