

Evaluation of Lipid Profile Changes in Pediatric Patients with Acute Mononucleosis

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Background: Acute Epstein–Barr virus (EBV) infection could lead to atherogenic lipid profile changes in adults; while there is no evidence about the children with Infectious mononucleosis (IM). The aim of this study was to evaluate the lipid profile of the children in acute phase of mononucleosis and two months after the recovery.

Materials and Methods: From 2010 through 2012, 36 children with IM aged 1-10 years were enrolled in a prospective cross-sectional study. Fasting serum total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL), and triglyceride level were measured during acute phase of the disease and after 2 months of the recovery.

Results: From 36 patients enrolled, 25 (69.4%) cases were male and the mean age of the patients was 4.1 ± 2.0 years. The mean of the total cholesterol level in the acute phase and 2 months after the recovery were 149.5 ± 35.3 mg/dL and 145.7 ± 30.6 , respectively ($P = 0.38$). However, the serum level of HDL cholesterol in patients after 2 months of recovery was significantly increased (37.9 ± 9.3 mg/dL vs. 28.5 ± 10.6 mg/dL, $P < 0.001$). The mean value of serum LDL cholesterol was significantly reduced, two months after recovery (81.4 ± 19.5 mg/dL, vs. 92.6 ± 28.8 mg/dL, $P = 0.009$). Furthermore, the serum triglyceride level was significantly reduced after the recovery (108.7 ± 36.9 mg/dL) compared with the acute phase (163.8 ± 114.3 mg/dL) ($P = 0.004$).

Conclusion: EBV infection in children could change lipid profile which is partially restored 2 months after the recovery.

Key Words: Atherogenic changes; Epstein–Barr virus; Infectious mononucleosis; Lipid profile; Pediatrics

Introduction

Several studies have indicated that atherosclerosis in adults begins from childhood [1]. The etiology of this phenomenon is multifactorial; the type of the diet, life style, genetic tendency and some underling diseases (e.g. diabetes, hypertension) are

known predisposing factors. In addition, infectious diseases especially chronic and recurrent ones (e.g. periodontitis) might be the other reason of atherosclerosis [1].

Infection with microorganisms such as *Chlamydia pneumoniae*, and cytomegalovirus, has been shown to increase the incidence of coronary artery disease (CAD), and these microor-

Received: April 24, 2016 **Accepted:** January 10, 2017 **Published online:** March 13, 2017

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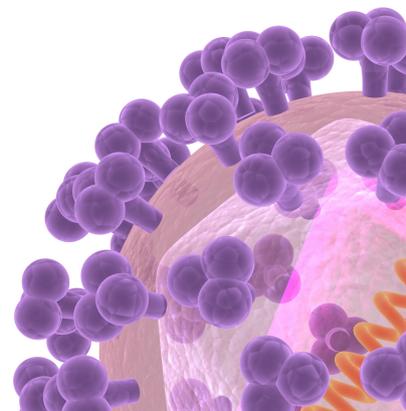
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ganisms have been detected in atherosclerotic plaques [2]. In addition, infections not directly related to vessels wall such as *Helicobacter pylori* and *Herpes simplex virus* infections; chronic bronchitis, and chronic dental infections, are also associated with increased incidence of CAD [2-4].

The changes seen during these infections include a reduction in the total cholesterol, high density lipoprotein (HDL), low-density lipoprotein (LDL), Apolipoprotein A-I, Apolipoprotein B and lipoprotein a (LP [a]) levels [3]. The increased level of triglyceride and Apo-lipoprotein E has also been documented in these infections [3]. It is reported that in some infections with microorganisms such as HIV, the level of small dense LDL, which has a greater atherogenic properties compared with LDL, increases and in some other infections (*e.g.* brucellosis) would not reach its normal level even after four months of the recovery [5, 6].

Infections also produce alterations in the composition and function of lipoproteins [7, 8]. The existing evidences suggest that change in lipoproteins level during infection is a part of acute phase response of innate immune system [6].

Increase in total triglycerides, triglyceride rich lipoproteins, small dense LDL, the activity of platelet activating factor acetyl hydrolase, sphingolipid rich lipoproteins, as well as HDL decrease are the changes which can lead to atherogenesis.

Besides, HDL metabolism alteration during infection results in a reduction of the HDL abilities in protection against atherogenesis through antioxidant and reverse cholesterol transport mechanisms. Such changes can explain the correlation of inflammation and infection with atherogenesis [9]. In addition, response to infection and inflammation increases the amount of oxidized lipids in serum, and induces LDL oxidation in the body.

Enhancement of LDL oxidation during infection and inflammation may cause atherogenesis, and can be a mechanism for the increase of coronary artery diseases in patients with chronic infection and inflammatory diseases [2].

Epstein-Barr virus (EBV) infection causes infectious mononucleosis, the most common symptoms of which are fever, pharyngitis, lymphadenopathy and organomegaly [10].

According to the findings of a study on adult patients, acute EBV infection could change the lipid profile which predisposes patients to atherogenesis [9]. However there is no supportive evidence of these changes among pediatric patients with acute infectious mononucleosis. The present study was conducted to evaluate the changes in serum lipid of pediatric patients with acute infectious mononucleosis and to compare them with the results obtained two months afterward. As far as we are aware,

the current study is the first research on the lipid profile changes in acute EBV infection in children.

Materials and Methods

This prospective cross-sectional study was conducted from 2010 through 2012 at Ali Asghar Children's Hospital, Tehran, Iran. The study was approved by the local ethics review committee for clinical research and informed consent was received from the children's guardians before enrollment. Thirty six Patients between 1- 10 years old with acute EBV infection, visited or admitted in the hospital, were enrolled in this study in a sequential manner.

The definite diagnosis of acute EBV infection in clinical-based suspected cases was carried out via laboratory tests of positive anti-EBV (IgM and/or IgG anti VCA Ab) and negative EBV antinuclear antibody (EBNA). Patients with, underlying liver and renal diseases, malignancy, hypo- or hyperthyroidism, sever failure to thrive (FTT), and patients treated with drugs affecting the serum lipid profile, were excluded from this study.

The age, gender and clinical manifestations of patients with acute EBV infection, including fever, lymphadenopathy, pharyngitis, and organomegaly, were recorded in a checklist for each patient. Fasting venous blood samples were collected to analyze the lipid profile level, including serum total cholesterol, HDL and LDL cholesterol, and triglyceride levels. The blood samples were collected at the peak of the symptoms in the acute phase of the disease, as soon as the EBV infection was confirmed, regardless of the hospital admission or in the outpatient set up. Based on a study of serum lipid profiles in Iranian children by Azizi et al., and the guidelines of United States National Cholesterol Education Program (NCEP), total cholesterol level less than 170 mg/dL, between 170- 199 mg/dL and more than 200 mg/dL were considered as desirable, at moderate risk, and high risk, respectively [11-13]. Also, LDL cholesterol levels less than 110 mg/dL, between 110-130 mg/dL, and more than 130 mg/dL were considered as desirable, moderate and high risk, respectively. Given the 10th percentile, the lower limit of HDL cholesterol level in Iranian children was considered 40 mg/dL. Regarding to the patients' age and gender, a serum triglyceride level less than the 90th percentile was considered in normal range. Thus, in boys and girls aging 1-4 years the triglyceride levels less than 85 mg/dL and 95 mg/dL and in 5-10 years, less than 70 mg/dL and 103 mg/dL were considered as normal, respectively [11].

Two months after the recovery, the measurement of lipid profile of the cases was repeated. The descriptive statistics, including frequencies, means and standard deviations were measured; the data were categorized to desirable and undesirable lipid profile categories according to the references [11-13], and were presented as numbers and percentages. As the data was related, for comparing lipid profile categories between baseline and two months later, Wilcoxon signed ranks test was performed. *P*-values less than 0.05 were considered as statistically significant. The relationship between lipid profile changes and acute phase values was evaluated using Pearson correlation test.

Results

Out of 36 children with infectious mononucleosis, 25 (69.4%) cases were male. The mean age of the patients was 4.1 ± 2.0 years (from 1 to 10 years) and 22 (61.1%), and 14 (38.9%) of them were within 1 to 5, and 6 to 10 years age groups, respectively. The body mass index (BMI) of all cases was within normal range and none of them was overweight or obese. Also none of them had family history of documented hyperlipidemia.

The most common clinical manifestations were fever (100%); exudative pharyngitis (55.6%) and cervical lymphadenopathy (52.8%). The frequency of the other manifestations is shown in Table 1.

The mean serum total cholesterol level of the patients was 149.5 ± 35.3 mg/dL in the acute phase of the disease. Twenty six cases (72.2%) had serum cholesterol level lower than 170 mg/dL and 4 patients (11.1%) had serum cholesterol level higher than 200 mg/dL. The mean serum total cholesterol level

Table 1. Frequency of signs and symptoms of the patients with acute infectious mononucleosis

Signs and symptoms	EBV positive (n = 36)
Fever	36 (100%)
Exudative pharyngitis	20 (55.6%)
Lymphadenopathy	19 (52.8%)
Splenomegaly	11 (30.6%)
Hepatomegaly	7 (19.4%)
Rash	1 (2.8%)
Seizure	1 (2.8%)

EBV, Epstein-Barr virus.

was 145.7 ± 30.6 mg/dL after 2 months of the recovery, which showed no statistically significant difference with the acute phase of the disease (*P* = 0.38).

Whereas the amount of serum HDL cholesterol revealed a significant increase 2 months after the recovery compared to the acute phase of the disease (37.9 ± 9.3 mg/dL *vs.* 28.5 ± 10.6 mg/dL, respectively *P* < 0.001). In the acute phase, 31 (86.1%) patients had HDL levels lower than 40 mg/dL; while after 2 months of the recovery, 20 (55.5%) cases showed serum HDL level lower than 40 mg/dL (*P* = 0.004) (Table 2).

In addition, the mean value of serum LDL significantly decreased 2 months after the recovery compared with the acute phase of the disease (84.1 ± 19.5 mg/dL *vs.* 92.6 ± 28.8 mg/dL, respectively, *P* = 0.009).

Serum triglyceride levels also decreased substantially after the recovery (108.7 ± 36.9 mg/dL *vs.* 163.8 ± 114.3 mg/dL, *P* = 0.004) (Table 2).

The Lipid profile in children with infectious mononucleosis showed no correlation with the age of the patients in acute phase and after the recovery (*P* ≥ 0.19). Moreover, there was no

Table 2. Lipid profile of patients with acute infectious mononucleosis at the acute phase and two months after the recovery

	Acute phase of infection (n = 36)	2 months after recovery (n = 36)	<i>P</i> -value
Total cholesterol (mg/dL)			
Normal (<170)	26 (72.2%)	28 (77.7%)	0.16
Moderate risk (170-199)	6 (16.6%)	6 (16.6%)	
High risk (>200)	4 (11.1%)	2 (5.5%)	
HDL-cholesterol (mg/dL)			
Normal (>40)	5 (13.8%)	16 (44.4%)	0.001
Decreased (<40)	31 (86.1%)	20 (55.5%)	
LDL-cholesterol (mg/dL)			
Normal (<110)	28 (77.7%)	32 (88.8%)	0.08
Moderate risk (110-129)	6 (16.6%)	4 (11.1%)	
High risk (>130)	2 (5.5%)	0	
Triglyceride (mg/dL)			
Normal ^a	8 (22.2%)	11 (30.5%)	0.18
Increased ^b	28 (77.7%)	25 (69.4%)	

^aSerum triglyceride level less than the 90th percentile was considered in normal range.

^bBased on more than 90th percentile value for gender and age. HDL, high-density lipoprotein; LDL, low-density lipoprotein.

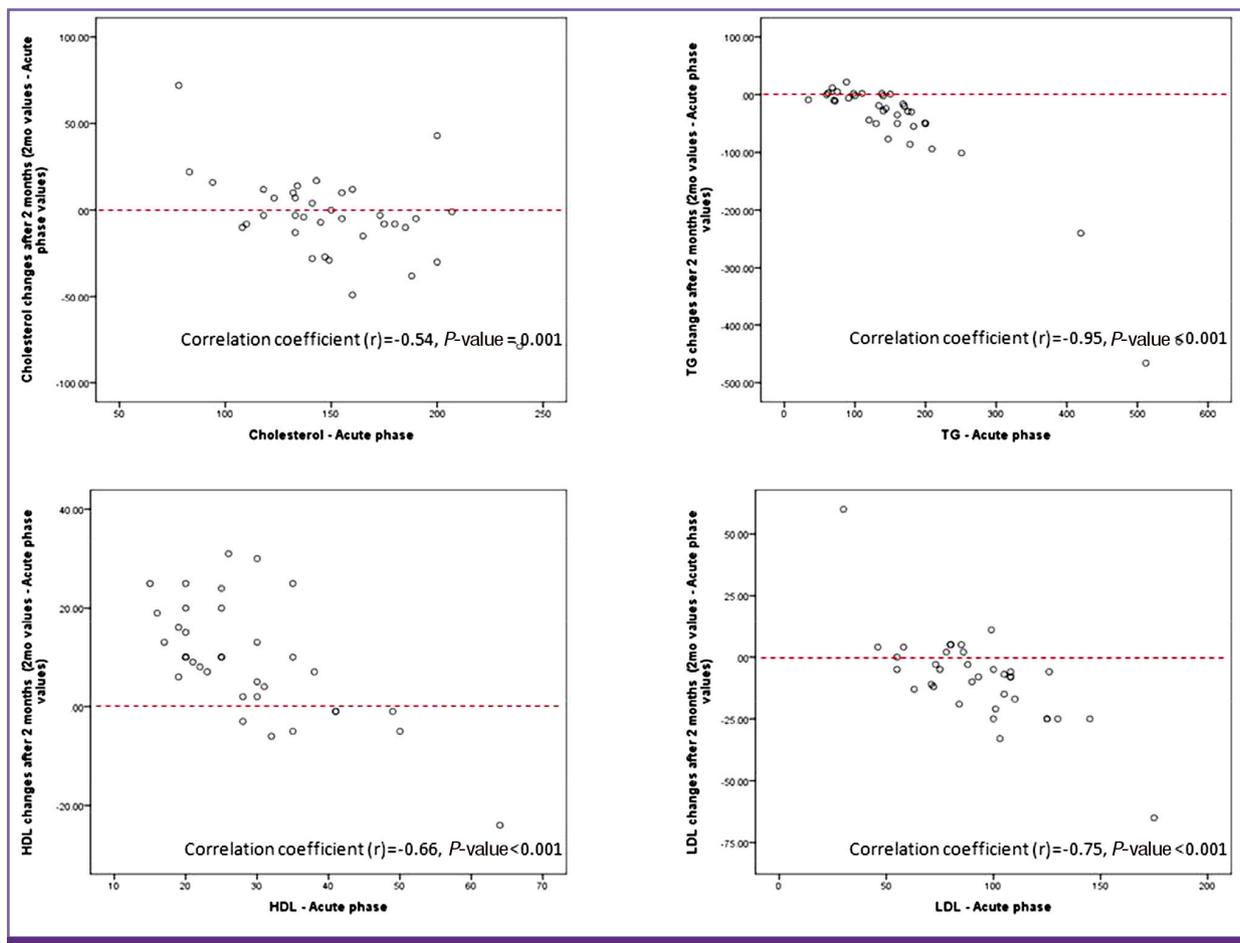


Figure 1. Distribution (mean and 95% confidence interval) of lipid profile in children with Epstein–Barr virus infection and relative atherogenesis risk categories in acute phase and two months after the recovery.

TG, triglyceride; HDL, high-density lipoprotein; LDL; low-density lipoprotein; mo, month.

correlation between lipid profile and the gender of the patients in acute phase of the disease and two months after the recovery ($P \geq 0.31$). Distribution (mean and 95% confidence interval) of lipid profile in children with Epstein–Barr virus infection and relative atherogenesis risk categories in acute phase and two months after the recovery phase was showed in Figure 1.

Lipid profile changes (case by case) revealed that those with more impaired values in the acute phase had more changes toward normal values at the recovery that were statistically significant for all evaluated parameters of lipid profile in our study (Fig. 2).

Discussion

During infection, the changes of the lipid and lipoprotein metabolism induce anti-inflammatory effects that contribute to

the host defense [7]. Besides the role of lipid transport, circulating lipoproteins participate in innate immunity by binding and detoxifying lipopolysaccharide and toxins of gram-negative, and lipoteichoic acid of Gram-positive bacteria [7]. On the other hand, the results of some studies in the literature reveal a relation between infection and atherogenesis [1, 5]. During the acute phase of the infection, the released cytokines induce a process that leads to changing the level of serum lipoproteins in a manner that resembles atherogenetic process; it is usually independent of the underlying infectious disease [7, 14, 15]. It seems that the infection-induced alterations initially protect the host from the harmful effects of bacteria, viruses, and parasites. However, if prolonged, these changes in the structure and function of lipoproteins will contribute to atherogenesis [5].

Our study revealed HDL increase, two months after the recovery compared with the acute phase of the infection which was in accordance with the result of Apostolou et al. study [9].

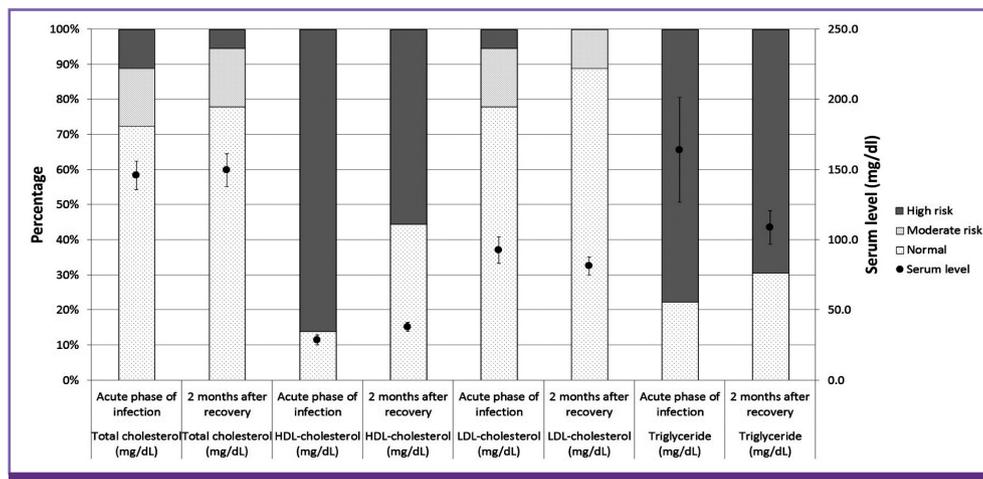


Figure 2. Correlation of lipid profile changes after two months of the recovery with acute phase values in patients with Epstein-Barr virus infection (More negative changes for higher values of cholesterol, TG and LDL and more positive changes for lower values of HDL).

TG, triglyceride; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

Indeed, acute infection not only decreases the number of HDL particles and concentration of HDL cholesterol, but also alters the structure of HDL particles, leading to loss of antioxidative actions of HDL [16]. These changes resemble the changes seen in the atherogenesis [17].

The LDL level in this study was increased in the acute phase of EBV infection which was not in accordance with Nassaji et al. and Apostolou et al. studies that reported no difference and decreased level of LDL in acute phase of the infection, respectively [7, 9]. Both of these studies were designed for the adults. In addition, Nassaji et al. studied the level of LDL only in patients with acute bacterial infections. However, some studies believe that the lipid profile changes during infection in pediatric patients might be different from those of the adults [18].

The level of triglyceride increased in the acute phase of infection in our study which was compatible with Apostolou et al. study [9].

In the current study, the mean value of serum total cholesterol in the acute phase showed no significant difference with the results of the 2 months after the recovery. This result was not compatible with the findings of Apostolou et al. research [9]. The discrepancy between these two results might be possibly due to shorter follow up of our cases (2 months vs. 4 months).

The current studies reveal that other infections might also have some effects on the patients' lipid profiles. Iscan et al. showed that the hospitalized children with infectious pharyngitis had dyslipidemia in the acute phase of the disease. The levels of serum total cholesterol, HDL, and LDL, decreased significantly in the acute phase of the disease while the serum tri-

glyceride levels increased slightly [19].

We approached to lipid profile serum levels by determining the mean serum level and also by categorizing in normal and abnormal groups as shown in Table 2. Comparing columns of the acute phase and two months after the recovery in Table 2, the changes might not have been shown clearly and specifically because the amount of changes may not be enough to alter the risk categories. It means that despite changes, which may be clinically important, the groups may not have altered because the changes have not reached to cut off points. Our objective might be shown better by Figure 1. In addition, according to the findings of the Figure 2 those with more impaired values, had more changes toward normal values two months after the recovery.

The present study revealed that the serum lipid profile changes of the acute phase of the EBV infection in children partially improves 2 months after the recovery and residual abnormal levels in the lipid profile might be due to short-term follow up of the patients. In the study of lipid profile evaluation in patients with acute EBV infection in adults, the lipid profiles of the patients improved significantly, four months after the recovery [9]. Some other infections also reveal the evidence of the lipid profiles improvement after the recovery [5, 19]. Therefore, defined lipid profile changes could be considered as a predictor of the acute phase of the infection/inflammation, and, returning of lipid profile indices to the baseline could be interpreter of finishing infection/inflammation process. Moreover, it should be considered that evaluation of lipid profile in patients with acute EBV infection should not be performed in

the acute phase of the disease; since the results cannot be judged and might be misinterpreted; and infection and inflammation could make temporary variations in the lipid profile indices.

Anti-VCA IgG solely is not a valuable test for diagnosis of acute EBV infection. In addition, anti-VCA IgM may persist for two weeks to three months [20]. So we used not only anti-VCA IgM but also EBNA test to increase the accuracy of acute phase diagnosis. Indeed, patients with negative EBNA but positive anti-VCA IgG and/or anti-VCA IgM were enrolled in the study. It means if the time of evaluation was so early for anti-VCA IgG, to become positive then cases with positive anti-VCA IgM and negative EBNA, were included. Also, if the time of evaluation was late acute phase then cases with negative anti-VCA IgM, and positive anti-VCA IgG but negative EBNA, were enrolled.

We admit our limitations as the sample size was few and the duration of follow up of the patients was less than the same study in adults which might have affected the results. It is therefore suggested to extend this investigation with more cases and longer follow up. According to some financial and technical limitations, we only measured some indices of the lipid profile.

The severity of the disease could affect the lipid profile level. However, only one case suffered from encephalitis that might have more severe disease than the others. It is one of the limitations of this study. In addition, serum lipid profile level, before and during the acute EBV infection, should be compared to reveal that the changes are the result of EBV infection. As far as we did not have the lipid profile level of the children before the disease, we compared the lipid profile level during acute phase and two months after the recovery of EBV infection that is another limitation of this study.

In conclusion, the children with acute infectious mononucleosis might experience some changes in lipid profile in the acute phase that improves partially two months after the recovery.

Hence, the assessment of the lipid profile in convalescence stage of infectious mononucleosis might be a predictor of the recovery.

Future studies for evaluating the pattern of lipid profile changes in other infectious diseases especially bacterial and fungal infections are suggested.

Conflicts of Interest

No conflicts of interest.

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