ORIGINAL ARTICLE ÖZGÜN ARAŞTIRMA

May HDL Cholesterol Level Have a Role in The Diagnosis of Kawasaki Disease?

HDL Kolesterol Düzeyinin Kawasaki Hastalığı Teşhisinde Olası Rolü

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Abstract

Introduction: Kawasaki disease (KD) is a multisystemic vasculitis that has no specific serum marker. The aim of our study is to evaluate whether the serum lipid profile, specifically HDL cholesterol (HDL-C) level, in KD differs from that in other febrile illnesses and if so, it can be used as a diagnostic tool in distinguishing KD from other febrile illnesses.

Materials and Methods: We examined prospectively 41 patients with KD (group 1) and 30 patients with febrile illness of viral or bacterial origin (group 2). The patients' demographic and clinical characteristics were analyzed. All blood samples were taken during the disease's acute phase. After fasting for four hours in infants and eight hours in young children, serum total cholesterol, HDL-C, triglyceride (TG), C-reactive protein (CRP), complete blood count, and other biochemical markers were determined. Group 1 was further divided into subgroups as incomplete vs complete cases and patients with vs without coronary artery involvement.

Results: Mean serum HDL-C level in KD group was significantly lower than in the febrile illness group (13.8±8.8 mg/dL vs 37.6±18.7 mg/dL, p <0.001). A statistically significant difference in TG levels was also present between both groups (group 1: 183±96 mg/dL vs group 2: 121±70 mg/dL, p=0.001). We detected a significant difference in terms of HDL-C levels, erythrocyte sedimentation rates, CRP, and TG levels between patients with febrile illness, complete KD, and incomplete KD (p <0.001; p=0.007, p <0.001, p=0.01, respectively). The most appropriate cut-off value of serum HDL-C level for affirming KD was ≤ 23 mg/dL. The area under the curve was 0.88 (95% confidence interval: 0.78-0.94, p <0.001).

Conclusion: The study showed that serum HDL-C level is lower in patients with KD than in those with acute febrile infectious disease. Presence of low serum HDL-C level (≤ 23mg\dL) may be helpful in establishing the diagnosis of incomplete KD.

Keywords
Kawasaki disease, coronary artery involvement, serum HDL-C level

Anahtar kelimeler
Kawasaki hastalığı, koroner arter tutulumu, serum HDL kolesterol

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Gereç ve Yöntem: KH tanısı alan 41 hasta (grup 1) ile viral veya bakteriyel kaynaklı ateşli hastalığı olan 30 hastanın (grup 2) değerlendirildiği prospektif bir çalışmadır. Çalışmaya dahil edilen hastaların demografik ve klinik özellikleri değerlendirildi. Tüm kan örnekleri hastalığın akut döneminde alındı. Bebekler için dört saat ve küçük çocuklar için sekiz saat aç kaldıktan sonra serum total kolesterol, HDL kolesterol (HDL-K), düşük yoğunluklu lipoprotein kolesterol (LDL-K), trigliserid (TG), C-reaktif protein (CRP), tam kan sayımı ve diğer biyokimyasal parametreler çalışıldı. Ayrıca KH ile takip edilen hastalar, inkomplet ve komplet vakalar ve koroner arter tutulumu olan ve olmayan hastalar olarak alt gruplara ayrılarak kendi içlerinde karşılaştırıldı.
Bulgular: KH grubunda ortalama serum HDL-K düzeyi ateşli hastalık grubundan anlamlı derecede düşük saptandı (13,8±8,8 mg/dL ve 37,6±18,7 mg/dL, p <0.001). Her iki grup arasındaTG düzeylerinde istatistiksel olarak anlamlı bir fark mevcuttu (grup1: 183±96 mg/dL ve grup 2: 121±70mg/dL, p=0,001). Ateşli hastalık, komplet KH ve inkomplet KH olan hastalar arasında HDL-K düzeyleri, eritrosit sedimantasyon hızları, CRP ve TG düzeyleri açısından anlamlı bir fark saptadık (p <0,001; p:=0,007, p <0,001, p <0,001, p <0,001, p=0,01, sırasıyla). KH tanısını doğrulamak için serum HDL-K düzeyinin en uygun eşik değeri ≤23 mg/dL idi. AUC 0.88 (%95 güven aralığı: 0,78-0,94, p <0,001) saptandı.
Sonuç: Çalışmamız, KH tanısı alan hastalarda, serum HDL-C seviyesinin akut ateşli enfeksiyon geçiren hastalara göre daha düşük olduğunu gösterdi. Düşük serum HDL-C düzeyinin (≤ 23mg\dL) varlığı, inkomplet KH tanısını koymada yardımcı olabilir.

Introduction

Kawasaki disease (KD), first defined in Japan, is now reported worldwide. It is an acute inflammatory multisystemic vasculitis of infants and young children. The disease is influenced by geographic and ethnic factors, and may recur (1). Even though its etiology is not fully determined, there are some clues to its infectious origin (2). The diagnosis of KD can be reached through laboratory-supported clinical findings (1). Although some laboratory findings can help establish the diagnosis, there is no specific serum marker for KD.

Clinical findings and the clinical course of KD may overlap with other febrile inflammatory diseases. The principal symptoms of KD may not be fully seen in incomplete cases, therefore the diagnosis continues to be challenging in incomplete cases (3,4). The diagnostic algorithm for evaluation of incomplete KD proposed in 2004 by the American Heart Association (AHA) had several limitations and was difficult to use in clinical practice (5). The 2017 guidelines have proposed a modified algorithm that is more meaningful and relatively easy to use (6). At the present time, the identification of serum or urine biomarkers of KD is an active area of research. Until a definitive diagnostic method exists, the best way for reducing diagnostic difficulties and enhancing diagnostic accuracy is to increase the number of supporting clinical and laboratory findings.

Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) remain the most important supportive laboratory markers for vascultis in KD. Most other laboratory findings (anemia, thrombocytosis, leukocytosis, hypoalbuminemia, high alanine aminotransferase) also have supportive roles in the diagnosis. Recognizing the disease in the acute period and treating it with intravenous immunoglobulin reduce the rate of coronary artery involvement and aneurysm from 25% to 5% (7). The presence of incomplete cases seems to increase the probability of coronary artery involvement by causing delay in diagnosis (8). Therefore, a better laboratory marker is needed especially for diagnosing incomplete KD.

It has been known that lipoprotein levels change during acute inflammatory response in infectious or autoimmune-rheumatic diseases, and newer studies have further reported that change in serum lipoprotein levels correlate with the type and severity of the inflammation (9,10). Several studies have shown that serum HDL cholesterol levels in both the acute phase of KD and other febrile illnesses correlate with classical inflammatory markers (11-13). However, studies that compare serum HDL levels between KD and other febrile illnesses are still scarce. HDL-C level can be used as a supporting evidence in the diagnosis of KD by observing its decrease during the acute inflammatory response.

The aim of the study is to evaluate whether the serum lipid levels, especially HDL-C, in KD differ from that in acute febrile illnesses of infectious origin during the acute phase and to investigate whether there is a correlation between lipid levels and the type and severity of the disease.

Material and Methods

We conducted the study between December 2010 and November 2018. Forty-four patients diagnosed

with KD (group 1) and 30 febrile patients with viral or bacterial infection (group 2) were evaluated prospectively. Of the patients included in group 2, 16 were diagnosed with upper respiratory tract infection, four with urinary tract infection, three with acute gastroenteritis, three with pneumonia, three with meningitis and one patient with acute tonsillitis. Patients in group 1 were further divided into subgroups as incomplete *vs* complete cases and cases with *vs* without coronary involvement. These subgroups were evaluated within themselves. Patients who have a disorder affecting lipid metabolism such as obesity or endocrine-metabolic diseases were excluded from the study. The demographic and clinical features of the patients were also evaluated. All blood samples were taken during the acute phase of the disease. After four hours of fasting for infants and eight hours for young children, serum total cholesterol (TC), HDL-C, low density lipoprotein cholesterol (LDL-C), triglyceride (TG), CRP, full urine analysis, complete blood count and other biochemical parameters were assayed.

Statistical Analysis

All statistical analyses were performed using IBM SPSS for Windows version 20.0 (SPSS, Chicago, IL, USA) and MedCalc for Windows, version 19.2.0 (MedCalc Software, Ostend, Belgium). Shapiro-Wilk's test was used to assess the assumption of normality. Continuous variables were presented depending on normal distribution with either mean ± standard deviation or (in case of no normal distribution) median categorical variables were summarized as counts. Comparisons of continuous variables between groups were carried out using independent samples t-test/Mann-Whitney U test, whichever was appropriate. Associations between continuous variables were determined by Pearson and Spearman correlation analyses and the association between two categorical variables was examined by chi-square test. Receiver operating characteristic (ROC) analysis was used to determine area under the curve (AUC) and cut-off values. Associations between continuous variables were determined by Spearman correlation analysis and the association between two categorical variables was examined by chi-square test. All statistical analyses were carried out with 5% significance and a two-sided p-value <0.05 was considered as statistically significant.

Results

The average age of patients with KD (group 1) was 4.04±2.6 years, and the average age of patients with infectious disease (group 2) was 4.0±3.3 years. Regarding the age, there was no significant difference between two groups (p=0.76). Male/female ratio was 22/19 in group 1 and 13/17 in Group-2 (p=0.53). Of 41 patients diagnosed with KD, 33 (81%) were diagnosed as complete and 8 (19%) as incomplete KD. Conjunctivitis was present in 34 (82.9%) patients, oropharyngeal changes in 37 patients (90%), rash in 35 (85.3%), lymphadenopathy in 31 (75.6%) and peripheral extremity changes in 23 (56%). Eight patients (20%) diagnosed with KD had sterile pyuria and 9 (23%) had gallbladder hydrops. In the echocardiographic evaluation; although coronary artery aneurysm was not found in any of 41 patients with KD, coronary dilation was observed in 8 patients (19.5%), pericardial effusion in 3 (7.3%), and mitral regurgitation in 2 (4.8%), no cardiac pathology was observed in 28 patients (68.2%). Average fever on admission was similar in both groups (group 1: 38.03±0.9 °C *vs* group 2: 38.4±0.4 °C, p=0.08) while average fever duration was higher in group 1 (7.36±3.8 days vs 3.2±2.4 days, p <0.001) (Table 1).

When patients were evaluated in terms of laboratory findings, group 1 had significantly higher median leukocyte and platelet counts than group 2 (p=0.01; p=0.03, respectively). Serum sodium, albumin and hemoglobin levels were lower in group 1 than in group 2 (p=0.001; p<0.001; p <0.001, respectively). Average HDL-C value was significantly lower in group 1 than in group 2 (13.8±8.8 mg/dL *vs* 37.6±18.7 mg/dL, respectively, p<0.001) (Figure 1).

A statistically significant difference in TG levels was also present between both groups. The average TG value was 183±96 mg/dL in group 1 and 121±70 mg/dL in group 2 (p=0.001). There was no significant difference between the group 1 and 2 in terms of LDL-C and TC levels (p=0.907; p=0.51, respectively). Mean CRP value was 13.8±12.4 mg/L in group 1, 3.6±5.4 mg/L in group 2 (p<0.001). CRP levels exhibited a negative correlation with serum HDL-C level in patient with KD (r=-0.36; p=0.002). There was a positive correlation between serum HDL cholesterol level and the febrile period of disease in group 1 (r=0.24; p=0.04) (Figure 2).

Table 1. Demographic, clinical characteristics and laboratory findings of group 1 and group 2

	Group 1 (n=41) mean ± SD	**Group 2 (n=30)** mean ± SD	p-value
Age (year)	4.04±2.66	4.08±3.62	0.76
Gender (male/female)	22/19	13/17	0.53
The duration of fever (days)	7.29±3.71	3.20±2.42	<0.001
Fever on admission (°C)	38.03±0.96	38.42±0.47	0.08
Hemoglobin (gr\dL)	10.46±1.33	12.03±1.17	<0.001
WBC (mm^3)	13,800±5,800	10,600±6,100	0.01
PLT (mm^3)	328,000±134,000	265,000±113,000	0.03
Serum sodium (mEq\L)	135±3	137±2	0.001
Serum albumin (gr\dL)	3.37±0.58	3.92±0.53	<0.001
Total Cholesterol (mg\dL)	131 41	144±49	0,51
HDL-C (mg\dL)	13.8±8.8	37.6±18.7	0.000
LDL-C (mg\dL)	82.2±34.4	82.4±30.4	0.9
Triglyceride (mg\dL)	183±95	121±70	0.001
ESR (mm/hr)	43.8±4.4	26.2±5.2	0.003
CRP (mg\L)	13.7±12.5	3.6±5.4	<0.001

SD: Standard deviation, WBC: White blood cell, PLT: Platelet count, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, HDL-C: High density lipoprotein-cholesterol, LDL-C: Low density lipoprotein-cholesterol

HDL-C, ESR, CRP and TG levels were significantly different between patients with febrile illness, complete KD, and incomplete KD (p=0.00; p=0.007, p=0.000, p=0.014, respectively). Duration of fever was significantly higher in patients with complete and incomplete KD than in those with febrile illness (p<0.001) (Table2). HDL-C and CRP levels in group 1 did not differ between patients with and without coronary artery involvement (Table 3). However, TG level was significantly higher in patients with coronary artery involvement (245.50±39.61 mg\dL, 164.1±15.06 mg\dL, respectively, p=0.03) (Table 3).

The ROC was performed to determine the predictive value of HDL-C level differentiation between KD and febrile illness of infectious origin. The most appropriate cutoff value of serum HDL-C level for affirming KD was ≤ 23 mg/dL. The AUC was 0.88 (95% confidence interval: 0.78-0.94, p<0.001). Sensitivity and specificity were 85.3% and 83.3%, respectively. The positive and negative predictive values of HDL-C at this cut-off level were 87.5% (95% confidence interval: 75.69-94.03) and 80.65% (95% confidence interval: 66.17-89.88). The ROC curve of HDL-C for diagnosing KD is displayed in Figure 3.

Discussion

KD is diagnosed through certain clinical findings, and does not yet have a specific-diagnostic biomarker. Studies on biochemical markers that can be used in the diagnosis of KD still continue (14). It can be challenging to establish the diagnosis of incomplete cases. Children with incomplete KD that remain undiagnosed and untreated for several days have a high risk for coronary artery involvement (8). While diagnosing KD in a patient with incomplete manifestation, one should consider additional laboratory and abnormal echocardiographic findings. Many clinical and laboratory signs not included in the principal diagnostic criteria have been used to support the diagnosis of KD (6). Perineal desquamation, sterile pyuria, hydrops of gall bladder, reactivation of the Bacillus Calmette-Guerin (BCG) injection site, peripheral arthritis, and myocarditis are other clinical findings. Anemia, thrombocytosis and hypoalbuminemia are the most accepted supporting laboratory findings in distinguishing KD (5). It is known that KD also affects the lipid profile. Studies on lipid profile in KD have focused on establishing the condition during the acute stage and evaluating the risks of cardiovascular morbidity in the chronic

Table 2. Demographic, clinical characteristics and laboratory findings of patient with Febrile illness, complete KD and Incomplete KD

	Febrile illness (n=30) mean ± SD	**Complete KD (n=33)** mean ± SD	**Incomplete KD (n=8)** mean ± SD	**p-value**
Age (year)	4.09±0.66	3.87±0.47	4,57±0.94	0.83
Gender (male/female)	13/17	19/14	3/5	0.53
The duration of fever (days)	3.20±0.44	7.18±0.65	7.75±1.47	<0.001
Fever on admission (°C)	38.4±0.8	38.0±0.1	38.1±0.3	0.16
Hemoglobin (gr\dL)	11.94±0.29	10.53±0.25	9.76±05	<0.001
WBC (mm^3)	10351±1.431	13,800±5,800	19,655±2,705	0.007
PLT (mm^3)	257,468±28,919	331,055±24,523	364,142±68,438	0.11
Serum sodium (mEq\L)	137±0.6	135±0.5	133±1.3	0.004
Serum albumin (gr\dL)	3.86±0.13	3.37±0.12	3.33±0.14	<0.001
Total cholesterol (mg\dL)	148±11	132±7	124±21	0.59
HDL-C (mg\dL)	36.5±4.1	16.4±5.3	14.7±1.8	<0.001
LDL-C (mg\dL)	85.5±7.5	84.8±6.3	73.6±18.9	0.61
Triglyceride (mg\dL)	131± 7	174±15	183.57±46.18	0.01
ESR (mm\h)	29.8±6.5	42.5±5.8	43.0±5.2	0.007
CRP (mg\L)	4.6±1.4	14.1±2.7	13.0±3.0	<0.001

SD: Standard deviation, KD: Kawasaki disease, WBC: White blood cell, PLT: Platelet, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate HDL-C: High density lipoprotein-cholesterol, LDL-C: Low density lipoprotein - cholesterol

Table 3. Demographic, clinical characteristics and laboratory findings of Kawasaki disease patient with and without coronary artery involvement

	Patient with CAI (n=8) mean±SD	**Patient without CAI (n=33)** mean±SD	**p-value**
Age (year)	4.59±1.11	3.86±0.45	0.57
Gender (male/female)	7/1	15/18	0.46
The duration of fever (days)	8.38±2.06	7.09±0.57	0.64
Fever on admission (°C)	38.2±0.1	37.2±0.3	**0.008**
Hemoglobin (gr\dL)	10.04±0.65	11.10±0.20	0.74
WBC (mm^3)	9,898±1,980	14,926±988	**0.02**
PLT (mm^3)	338,925±51,973	325,303±24,045	0.98
Sodium (mEq\L)	134±1	136±0.4	0.23
Albumin (gr\dL)	3.39±0.20	3.38±0.09	0.56
Total cholesterol (mg\dL)	157±19	134±6	0.09
HDL-C (mg\dL)	15.2±4.04	14.7±1.6	0.88
LDL-C (mg\dL)	95.7±19.1	81.5±4.5	0.46
Triglyceride (mg\dL)	245±39	164±15	**0.03**
ESR (mm\h)	41.8±14.9	36.6±3.7	0.43
CRP (mg\L)	12.9±4.5	9.8±1.6	0.46

SD; Standard deviation, HDL-C; High Density Lipoprotein-Cholesterol, LDL-C; Low Density Lipoprotein - Cholesterol, TG: triglyceride, TC: total cholesterol, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, Hgb: hemoglobin, WBC: White blood cell, PLT: platelet, CAI; Coronary artery involvement

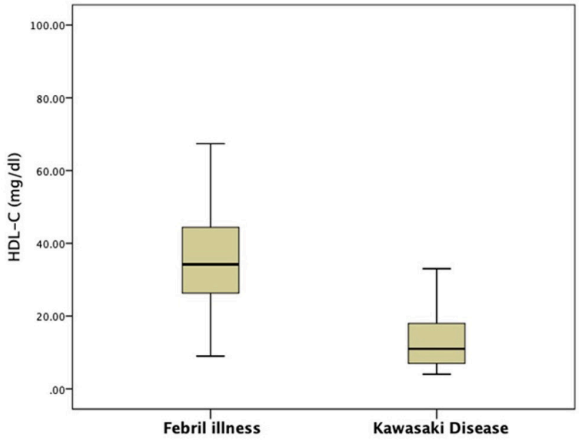

Figure 1. The box plot showing serum HDL-C level (mg/dL) in patient with Kawasaki disease and febrile illness.

stage. Research on the diagnostic ability of lipids has remained insufficient. In the present study we evaluated whether HDL-C has any diagnostic utility in KD, and whether it would be as reliable as classical supporting laboratory findings. Studies on lipid profile in recent years, and our own clinical experiences have suggested that serum HDL-C level, which is known to decrease during the acute inflammatory response, can be used to support the diagnosis of KD. No consensus exists regarding clinical usefulness of serum HDL-C level as a marker especially for patients with incomplete KD.

During the acute phase response, CRP can interact with various molecules, such as bacterial capsules, membrane phospholipids, complement proteins and lipoproteins (LDL-VLDL cholesterol) (15). Cytokine and interleukin induced-change of hepatic lipase activity in the liver and lipoprotein lipase activity in the peripheral tissue, use of LDL-C, VLDL-C as a ligand by CRP suggest that lipoproteins play an active role during the acute phase response. However, these changes do not fully explain the physiopathology of the alteration in the lipid profile. It is not clear whether change in lipid profile is a conservative response exhibited by the organism against inflammation or a secondary disorder that develops following inflammation.

A negative relationship between the changes in serum HDL and CRP levels has been reported in the acute period of KD and febrile infectious diseases. The study of Ou et al. (12) encompassing 119 patients with KD indicated that decrease in HDL-C level and increase in CRP level were more prominent in patients with coronary artery involvement than in those without. Connelly et al. (10) reported that decrease in HDL-C levels were more marked in KD patients than in those with acute infectious disease. Moreover, they reported that the decrease in HDL-C level was more prominent in patients with coronary artery involvement and it continued into the subacute phase of the disease. We found that HDL-C level was lower in patients with KD than in those with febrile infectious disease, which supports Connelly's study. But contrary to Connelly's study, we didn't find any differences in HDL-C levels between patients with and without coronary artery involvement. Interestingly, we determined that serum

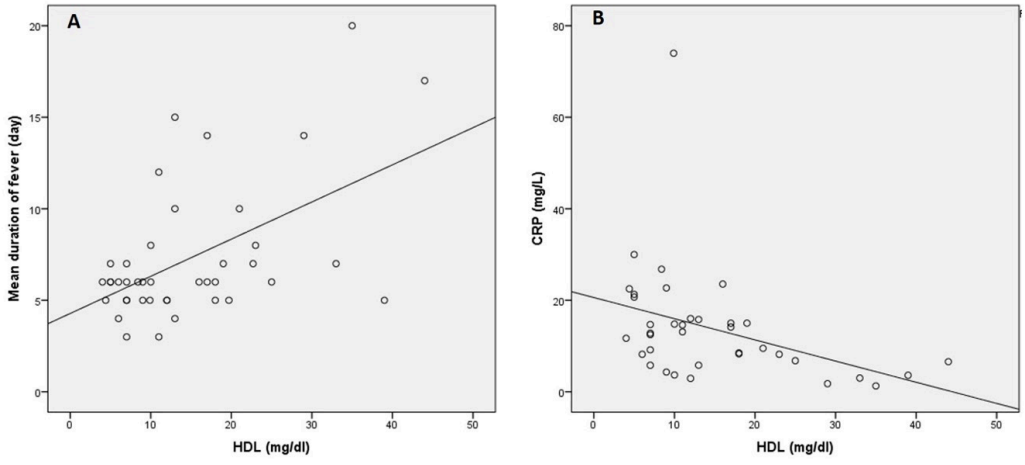

Figure 2. A. Positive correlation in patient with KD between HDL-C level and mean duration fever is shown in figure 2A. **2B.** Negative correlation in patient with KD between HDL-C and CRP level is shown in figure 2B.

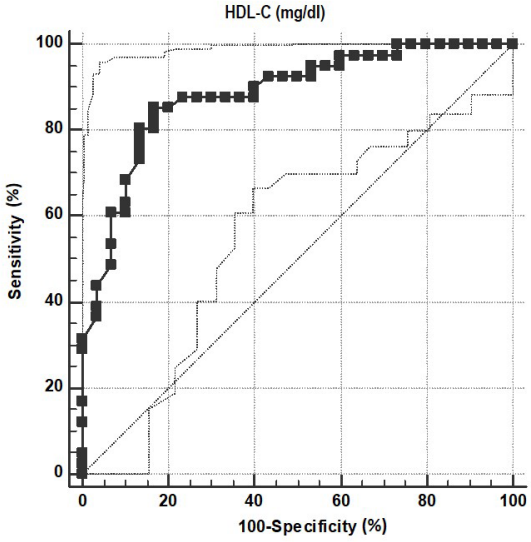

Figure 3. According to receiver operating characteristic curve, a HDL-C level of 23 mg/dL or less was the best cut-off value for predicting Kawasaki disease (AUC:0.88, p <0.001) with sensitivity 85.3%, specificity 83.3%.

TG level was significantly higher in KD patients than in those with febrile illness. Furthermore, mean TG level was significantly higher in patients with coronary artery involvement than in those without involvement. Some studies indicate that elevated TG level is associated with endothelial inflammation and dysfunction (16,17). These observations make one think that high TG levels in patients with KD can predispose to coronary involvement.

We found a negative correlation between HDL-C and CRP levels in both groups. The negative correlation between CRP and HDL-C detected in our study could suggest that decreased levels of HDL-C reflect the severity of inflammation. Additionally, in KD patients, HDL-C level was positively correlated with the duration of fever. Based on this observation, we think that the diagnostic value of HDL-C in KD patients decrease as the duration of fever gets longer. Therefore, the use of low HDL-C level as a diagnostic marker for KD may be feasible merely during the acute phase of the illness.

While HDL-C levels during the acute phase of inflammatory diseases have exhibited consistent and marked decrements in previous studies, LDL-C level exhibited decrement in one study and increment in another (18,19). We found no change in LDL-C level in both groups.

Studies regarding the lipid profile in KD have focused mostly on its prognostic value. However, there are few studies on its diagnostic value. A study of Newburger et al. (20) indicated that increased ratio of total cholesterol\HDL-C levels, in addition to decreased HDL-C level, was also meaningful in patients with KD but they did not determine a cut-off value. We propose that a HDL-C level cutoff value below 23mg\dL is feasible and acceptable in supporting KD with 85.37% sensitivity and 83.33% specificity. Our result suggests that serum HDL-C level can be used as a supportive finding in KD, just as other laboratory markers (ESR, CRP, thrombocytosis, and anemia etc.) recommended in the AHA guidelines.

Huang et al. (21) studied on another biochemical markers in patients with KD. They found a cutoff value of 2 using the ratio of haptoglobin\apolipoprotein A-1 for diagnosing KD with 89.7% sensitivity and 85.6% specificity. The study of Lin et al. (22) examined KD patients with regard to a relationship between altered lipid profile and further atherosclerosis. They did not find a long lasting effect on HDL-C profile in pediatric and adult patients who have KD.

Conclusion

The study showed that serum HDL-C level is lower in patients with KD than in those with acute infectious febrile disease. Serum HDL-C levels combined with clinical characteristic findings may help differentiate incomplete KD cases from other febrile illnesses of infectious origin. Our results showed that the cutoff value of 23 mg\dL HDL-C level has 85.37% sensitivity and 83.33% specificity for detection of KD. We did not detect a link between coronary artery involvement and HDL-C levels; therefore, the prognostic value of HDL-C level remains controversial. We also found that KD patients with coronary artery involvement have a higher TG levels than those without coronary involvement and those who had acute infectious disease. Further studies are needed to identify the prognostic value of higher TG levels in predicting the possibility of coronary artery involvement in KD.

Ethics

Ethics Committee Approval: Kocaeli University Non-Invasive Clinical Research Ethics Committee (approval number: KÜ GOKAEK 2018/7 date: 18.04.2018)

Conflict of Interest: No conflict of interest was declared by the authors.

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