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# Relationship Between Gallbladder Distension and Lipid Profiles in Kawasaki Disease

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## ABSTRACT

**Background and Objectives**: Kawasaki disease (KD) is an acute systemic vasculitis in children which causes coronary arterial dilatation (CAD) and gallbladder distension (GBD). There is a dearth of investigating the relationship between the severity of KD and GBD with lipid profiles. **Subjects and Methods**: A total of 80 patients with 'complete KD' who were diagnosed from January 2005 to May 2009 was enrolled in this study. Serum cholesterol {total, high density lipoprotein-cholesterol (HDL-C) and low density lipoprotein-cholesterol (LDL-C)}, triglyceride (TG), complete blood count, inflammation markers {erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)} were measured at the time of admission during febrile period. Echocardiography and abdominal sonogram were performed in all patients to determine CAD and gallbladder size. According to GBD, patients with KD were classified as patients with GBD and patients without GBD. Between two groups, demographic and clinical data were analyzed. **Results**: The serum level of LDL-C was significantly lower in patients with GBD (p=0.03) compared with patients without GBD or febrile control. There was no significant difference in inflammatory indices between patients with GBD and patients without GBD. GBD was not significant risk factor of CAD in this study (odds ratio=2.0, 95% confidence interval=0.82-5.3, p=0.16). **Conclusion**: This is the first study that highlights the relationship between the GBD and lipid metabolism in patients with KD. This study provides clinical insights about potential mechanism underpinning the relationship between the GBD and lipid metabolism. **(Korean Circ J 2010;40:137-140)**

**KEY WORDS:** Gallbladder disease; Lipids; Coronary artery disease; Children.

## Introduction

Kawasaki disease (KD) is an acute systemic vasculitis of childhood affecting small- and medium-sized arteries.[1)] The inflammatory reaction of KD can lead to vasculitis of coronary arteries, hence this disease is considered a leading cause of acquired heart diseases in childhood in developed countries.[2)] Characteristic clinical features of KD include prolonged fever, bilateral bulbar nonexudative redness, mucocutaneous changes of lips and mouth, transient polymorphous rash, erythematous swelling of palms and soles, and cervical lymph node enlargement more than 1.5 cm.[1)] Other manifestations of KD that reflect its systemic vasculitis nature are sterile pyuria, hepatitis, GB hydrops, arthritis, and aseptic meningitis.[3)]

Among systemic findings of KD, gallbladder distension (GBD) is observed in about 8.8% of patients through ultrasonogram.[4)] Abdominal sonogram is a routine diagnostic work up for KD,[5)] however few case reports about the significance of GBD in patients with KD have been published. Previous studies suggested that inflammation of biliary tracts may explain the phenomenon of the GBD in KD.[6)] Suddleson et al.[5)] reported that GB hydrops could be an early diagnostic marker in atypical KD.

GBD has been reported in various autoimmune dise-

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ases such as rheumatoid arthritis, antiphospholipid syndrome, Henoch-Schönlein purpura and systemic lupus erythematosus.[7][8] Gallbladder is the main organ of lipid metabolism. When there is inflammation in the gallbladder, the endothelial function of gallbladder for recycling of lipid could be decreased.[9-11] Several reports suggested that the patients with coronary arterial lesions have the lower serum levels of total cholesterol (TC), high density lipoprotein-cholesterol (HDL-C), and apo A-I, A-II and B than those of patients without coronary arterial lesions during the acute stages of KD.[10][12] While low density lipoprotein-cholesterol (LDL-C) or Triglyceride (TG) are controversial among studies.[9][13-15] Taken together with the previous findings, if the inflammatory processes are vigorous, the endothelial functions of gallbladder could be decreased due to inflammatory changes of GB, pathologic bile duct proliferations or inflammatory cell interactions. As a consequence lipid profiles may be changed until the inflammation is subsided, which usually takes two weeks after acute phase.

Recently coronary arteritis with unbalanced lipid profiles are explained as aberrant autoimmune reactions[16] and the increased levels of proinflammatory cytokines such as tumor necrosis factor-$\alpha$ (TNF-$\alpha$), interleukin-6 (IL-6), and IL-1$\beta$.[17][18] Lipid profiles as well as C-reactive protein (CRP) may be related with the severity of inflammatory autoimmune vasculitis.[13][17]

The purpose of this study is to assess the association of severity of KD and GBD with lipid profiles.

## Subjects and Methods

### Patient population

A total of 80 patients who were diagnosed as complete KD in Wonju Christian Hospital from January 2005 to May 2009 were enrolled in this study. The demographic characteristics of patients including age, gender, and previous KD history were recorded at the time of admission.

They met the diagnostic criteria for KD and were followed up by the same cardiologist. Echocardiography was performed in all patients to examine coronary arterial dilatation (CAD) and any other cardiac lesions. We determined CAD according to criteria as following. If the patient is younger than 5 year old, according to the body weight, if it is over 15 kg, CAD is defined as more than 3.0 mm, if it is less than 15 kg, as more than 2.5 mm. In patients whose age is above 5 years of age, CAD is defined as more than 4.0 mm.

Abdominal sonogram was performed in all patients to measure GB size by the same radiologist. GB size was measured by length and width.[20] GBD was defined as more than 2 standard deviation of the age matched average values of length and width.

Patients with KD were classified into two groups according to the GB size, patients with GBD and patients without GBD. Febrile controls were recruited. The febrile controls was composed of 20 patients who were admitted with urinary tract infection and taken abdominal sonogram.

Fasting serum TC, HDL-C, LDL-C, TG, complete blood count, erythrocyte sedimentation rate (ESR), and CRP were measured at the time of admission when the patients had fever.

### Statistical analysis

The SAS version 9.1 (SAS Institute Inc., Cary, NC, USA) was used to perform all statistical analysis. The demographic data and lipid profiles from each group were compared using analysis of variance. The data of inflammatory indices from patients with GBD group and patients without GBD group were compared using t-test. Pearson correlation analysis was used to assess the correlation between GBD and CAD with adjustment of age.

Statistical significance was set at $p<0.05$ was considered statistically significant.

## Results

The demographic characteristics of study population are shown in Table 1. Out of a total 80 patients with typical KD, 26 patients had GBD and 54 patients had no GBD. There were 3 cases of relapse and 2 cases of refractory KD. Among patients with GBD, seven patients had abdominal pain whose liver enzyme levels were elevated. Sixteen patients had elevated levels of aspartate aminotransferase or alanine aminotransferase. Abdominal mass was not evident in all children.

The main difference in lipid profile between two groups was LDL-C level. In acute phase of KD, LDL-C level was significantly lower in the GBD group ($p=0.0030$). There was no significant difference in TC, TG, HDL-C, or TC/HDL-C levels among three groups (Table 2).

There was no significant difference in inflammatory indices between patients with GBD and patients without GBD (Table 3). In addition, there was no significant difference of frequency of intravenous immunoglobulin (IVIG) treatment between two groups. One relapse case and one refractory KD were included in GBD group; two relapse cases and one refractory KD were in-

**Table 1.** Demogrphic characteristics of patients with Kawasaki disease and febrile controls

| Parameter | Patients with GBD | Patients without GBD | Febrile control |
|---|---|---|---|
| Number | 26 | 54 | 20 |
| Mean age (year) | 1.88±2.27 | 2.33±1.98 | 1.79±2.32 |
| Gender ratio (M:F) | 23:3 | 29:25 | 9:11 |
| CAD | 17 | 10 | 0 |

GBD: gallbladder distension, CAD: coronary arterial dilatation

**Table 2.** Lipid profiles among patients with GBD, patients without GBD, and febrile controls

| Parameter | Patients with GBD | Patients without GBD | Febrile control | p |
|---|---|---|---|---|
| TC (mg/dL) | 145.62±31.76 | 147.41±34.08 | 148.65±33.44 | 0.9520 |
| TG (mg/dL) | 126.58±52.24 | 110.56±48.38 | 136.55±93.64 | 0.3850 |
| HDL-C (mg/dL) | 33.77±15.26 | 34.48±12.32 | 40.55±14.58 | 0.2231 |
| LDL-C (mg/dL) | 72.65±23.29 | 82.56±30.08 | 101.93±30.06 | 0.0030 |
| TC/HDL-C | 5.61±4.44 | 4.72±1.63 | 4.19±1.89 | 0.2677 |

GBD: gallbladder distension, TC: total cholesterol, TG: triglyceride, HDL-C: high density lipoprotein-cholesterol, LDL-C: low density lipoprotein-cholesterol

**Table 3.** Comparison of inflammatory indicies in patients with Kawasaki disease according to gallbladder distension

| Inflammatory indicies | Patients with GBD | Patients without GBD | p |
|---|---|---|---|
| WBC (count/$\mu$L) | 13358.52±7025.35 | 12220.37±4941.17 | 0.3253 |
| ESR (mm/hour) | 62.84±37.91 | 66.81±35.15 | 0.6942 |
| CRP (mg/dL) | 7.04±6.43 | 6.22±6.04 | 0.6325 |
| Platelet (count/$\mu$L) | 402703.70±123551.45 | 413111.11±217946.59 | 0.9177 |

GBD: gallbladder distension, WBC: white blood cell, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein

cluded in no GBD group.

When we determined the GBD more than 2SD of mean GB size according to age, GBD was not proved to be a significant risk factor of CAD (odds ratio=2.0, 95% confidence interval=0.82-5.3, p=0.16). When stratified with age, GB width and right coronary artery (RCA) size only showed significant correlation (p<0.001); however, other parameters did not show significant associations.

## Discussion

Kawasaki disease is an acute febrile illness of childhood characterized by clinical laboratory and histopathological features of systemic small- and medium-sized vascular inflammation.[20] Marked activation of the immune system during acute phase of KD such as increased cytokine production by activated effector cells leads to coronary arterial lesions.[21-23] The treatment of KD is based on two goals, the reduction of inflammation and prevention of the long-term sequelae. High-dose IVIG therapy with aspirin is effective in resolving inflammation and reducing occurrence of coronary arterial abnormalities.[24][25]

Immunoregulatory mechanisms of IVIG in KD are explained as following: 1) modulation of cytokine production, 2) neutralization of bacterial superantigens or other etiologic agents, 3) augmentation of T-cell suppressor activity, 4) suppression of autoantibody synthesis, and 5) provision of anti-idiotypic antibodies.[26]

Lipid profiles may be changed by endothelial dysfunction of the inflammed gallbladder, which can be one of the risk factors of coronary arterial disease.[13] In this study, only LDL-C level was significantly lower in the patients with GBD. Other lipid profiles did not show any difference among three groups. Because we detected lipid profiles in acute phase and LDL-C level was decreased, which is compatible result of Chiang et al.[15] However, there are some reports that LDL-C level is higher in patients with KD than controls.[9][13] These studies were done in subacute phase of KD[13] and the mean age was higher than our study (7.6 year old vs. 2.68 year old).[9] The cause of transient decrease in LDL-C level is unknown. However, oxidized LDL-C is involved in the pathogenesis of vasculitis so transient consumption of LDL-C in acute inflammation may be suggested as a possible cause. Fast consumption and late synthesis due to GB dysfunction are yet to be determined in KD.

Various inflammatory indicies such as the count of white blood cells, ESR, and CRP were measured. In this study, GBD failed to show the association with inflammatory indices. GBD is thought to be secondary change from processes of vasculitis in the GB wall or an inflammatory change of bile duct.[7] Therefore, GBD may be considered to be an another candidated clinical biomarker of inflammation in KD.

Statin, hydroxymethylglutaryl coenzyme A reductase inhibitor, was proved to be effective to reduce cholesterol levels and improve surrogate inflammatory markers of atherosclerosis or cardiovascular disease.[27] According to Huang et al.[28] a short-term statin therapy appeared to significantly improve chronic vascular inflammation and endothelial dysfunction without adverse effects in children who were complicated by coronary artery abnormality after KD. Before administering statin in KD, the basic data about lipid metabolism in KD would be required first. As far as we know, our report is the first study to investigate an association between GBD and CAD. We demonstrated that there was a significant relationship between GB width and RCA diameter (p<0.001). Although this relationship was apparent when we stratified our subjects according to the age factor, this may be explained by anthropometical changes in GB and RCA. However, this assumption should be elucidated

with a larger sample size and robust experimental design.

Several additional shortcomings of this study should be considered in future research. One is that it was a retrospective study performed in a single tertiary medical center. The second limitation is that the change of lipid profiles in subacute phase was not checked. We could not observe the changes of lipid profiles in subacute phase of KD and compare with those of acute phase. The third limitation is an age factor. In the present study, we included infants who have reversible GBD, which may have confounded accurate measurement of GB size due to fasting, intravenous nutrition, and obesity beside inflammation.[29] Therefore, it would be limited to generalize our findings to the relationship between GBD and inflammation to interpretation of GBD in infants with KD.

Further studies should examine the long-term lipid profiles and inflammatory biomarkers in KD, which will provide invaluable information for effective management of chronic sequelae of KD. In conclusion, although our data failed to prove that GBD could be another biomarker of KD, they may be valuable as a basic study for suggesting the association of lipid profiles, GBD, and inflammatory markers of KD.

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