

RESEARCH LETTER

Significantly Lower Immunoglobulin M Levels 6 Months After Disease Onset in Patients With Kawasaki Disease With Coronary Artery Lesions

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Intravenous immunoglobulin (IVIG) administration can up-regulate immunoglobulin M (IgM) in Kawasaki disease (KD). McCrindle et al indicated an association between the lower serum IgM levels of patients with KD and the greater z score of coronary arteries.¹ Patients with KD have significantly more hospital admissions due to infection than control subjects.² Therefore, we are concerned about whether the decline of IgM levels will continue.³ *FCMR*-encoded *FcγR* is a receptor of IgM. In our recent report, we found that low *FCMR* mRNA expression was found in the leukocytes of patients with KD 6 months after disease onset.⁴ Some IgM antibodies have been thought to participate in the pathophysiology of coronary artery disease for its regulatory function on vascular remodeling. Previous studies have revealed that anti-phosphorylcholine IgM levels decreased in patients with major acute cardiovascular events. In this study, we aimed to explore the role of IgM in the prognosis of KD.

The data are available from the author upon request. We enrolled 40 sets of serially collected KD samples that were collected before IVIG treatment (KD1) and at multiple points after IVIG treatment (3–7 days, KD2; 3 weeks, KD3; and 6 months later, KD4), as well as 23 age- and sex-matched non-KD controls. After thawing plasma stored in a –80°C refrigerator, we performed nephelometric quantification to measure the value of IgM in plasma using the BNP ProSpec nephelometer (Siemens Healthcare Diagnostics) according to the

manufacturer's instructions. The study was approved by the institutional review board of Kaohsiung Chang Gung Memorial Hospital (201802059A3).

KD criteria was defined by the guidelines published by the American Heart Association. Coronary artery lesions (CAL) were defined by the Japanese Ministry of Health criteria or a z score ≥ 2.5 . Echocardiograms were obtained during admission for KD to evaluate z scores at the acute stage. Coronary artery dimensions of Taiwanese children aged <6 years were measured and normalized according to z scores from the database on body surface area.⁵ All echocardiographic images were evaluated by cardiologists who were not blinded to the patients' clinical status of KD but were unaware of their IgM levels. We did not evaluate the intra- or interexaminer variability. Certificated pediatric cardiologists surveyed coronary arteries according to the reference.⁵

Of the 40 patients with KD, 20 with CAL and 20 without CAL were enrolled by case-control method. Six months after IVIG treatment, patients with CAL appeared to have lower IgM compared with patients without CAL (89.01 \pm 5.41 versus 122.35 \pm 10.50 mg/dL, respectively; $P=0.012$ using the Mann-Whitney *U* test) (Figure [A]). We also found that patients with CAL had lower IgM values than patients without CAL at KD2 (110.24 \pm 7.52 versus 162.88 \pm 18.60 mg/dL, respectively; $P=0.018$). We found no significant difference in IgM levels between KD1 and controls. The IgM levels

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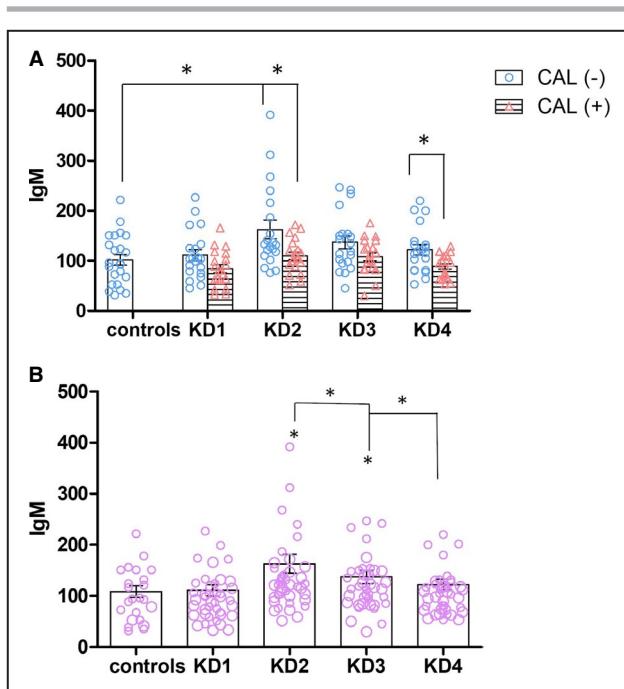


Figure 1. Comparison of immunoglobulin M (IgM) values among patients with Kawasaki disease (KD) before intravenous immunoglobulin (IVIG), after IVIG, and controls. **A**, The coronary artery lesions (CAL) group demonstrated a significant decrease in IgM values at KD2 and KD4. Nonparametric statistics using the Mann-Whitney *U* method revealed that the IgM levels in the controls and KD2 patients without CAL were 102.02 ± 10.63 and 162.88 ± 18.60 mg/dL, respectively ($P=0.010$). **B**, Despite significantly higher mean IgM levels at KD2, the IgM levels gradually declined but remained significantly greater than the pretreatment levels at KD3. Follow-up of 40 of these children revealed normalization of IgM levels during the subsequent 6 months. A borderline significance was found in IgM levels between controls and KD2 patients ($P=0.050$, Mann-Whitney *U* method). The IgM levels did not differ significantly between controls and KD1, KD3, or KD 4 patients. The error bars represent standard error. * $P < 0.05$ compared with IgM at KD1. KD1 indicates within 24 hours before IVIG treatment; KD2, 3 to 7 days after IVIG; KD3, 3 weeks after IVIG treatment; and KD4, 6 months after IVIG treatment.

in patients with CAL before IVIG tended to be lower than in patients without CAL but did not reach statistical significance (84.19 ± 7.99 versus 111.38 ± 10.99 mg/dL, respectively; $P=0.068$). The low number of cases in this study likely explains the lack of statistical difference. In patients with KD, the highest IgM level was found in KD2 using a paired-sample *t* test, followed by KD3 (Figure [B]). Before and after 6 months of IVIG treatment, IgM levels revealed no significant difference.

A higher *z* score of the left anterior descending coronary arteries at the acute stage and a lower IgM level measured at all time points (KD1–4) were significantly correlated by Pearson correlation ($P < 0.05$). Only 2 patients had *z* scores of left anterior descending coronary arteries ≥ 2.5 . The KD2 and KD4 IgM levels in patients

with *z* scores of the left main coronary artery (LCA) ≥ 2.5 ($n=17$) were significantly lower than those with *z* scores < 2.5 ($n=23$; $P=0.037$ and 0.003 , respectively). Multiple linear regression showed that the change of KD4 IgM was negatively correlated with higher *z* scores of the LCA, left anterior descending coronary arteries, and the proximal right coronary artery after adjusting for the effects of baseline, age, and *z* scores (adjusted $R^2=0.252$, 0.287 , and 0.285 ; $P=0.043$, 0.016 and 0.017 , respectively). The IgM change from baseline to KD4 was significantly different between patients with KD with and without LCA dilatations by linear regression, with baseline and age as covariates (adjusted $R^2=0.255$, $P=0.040$). Additional factors associated with a greater *z* score of the LCA and right coronary artery during admission included lower IgM levels at KD2 and KD4. The use of corticosteroids in acute KD ($n=21$, 4 in the non-CAL group, 17 in the CAL group) did not influence IgM levels ($P > 0.05$ using the Mann-Whitney *U* test at KD1–4).

The patients who are CAL-positive and CAL-negative seem to have different IgM dynamics. Interestingly, patients with and without LCA dilatations seem to have different IgM dynamics in the recovery period. This study suggests that the decrease of KD4 IgM was correlated with higher *z* scores of the coronary arteries.

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Disclosures

None.

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