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Letter to the Editor

Establishment of Reference Intervals of Serum Immunoglobulins in Healthy Korean Adults

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To the Editor,

It is known that humoral immunological disease (excess or deficiency) is caused by quantitative/functional deficiency in or excess of total immunoglobulins (*e.g.*, immunoglobulin (Ig) G, A and M) and/or IgG subclasses (IgGSCs). Although the prevalence of this disease is low in adults, IgG3 subclass deficiency (IGG3SCD) has been found to be associated with asthma exacerbation in adult asthmatic patients, and IgG4-related disease has been reported in patients with asthma.[1,2] Considering that age, sex and ethnicity could affect IgG and IgGSC concentrations, it is essential to establish proper cutoffs each of Ig and IgGSC levels in our population.[3] To evaluate IgGSC concentration, turbidimetric immunoassay (TIA) and nephelometry (Nep) have been widely used in practice in which Nep is thought to be more sensitive but expensive than TIA. The present study aimed to determine the reference interval (RI) each of Igs and IgGSCs in Korean adults for the diagnosis and monitoring of patients with humoral immunologic disease including IgG3SCD-or IgG4-related disease. This study was approved by the Ajou University Institutional Review Board, and all informed consent forms were obtained from all participants (AJIRB-Med-SMP-18-207).

Two-hundred healthy adult volunteers with no evidence of immunological disease, including immunodeficiency or excess in Ig-related diseases, were enrolled and classified into 3 groups based on age and sex at the same ratio (20–39/40–59/over 60 years, n = 80/80/40, respectively). The serum levels of IgG/A/M and IgGSCs were simultaneously measured using 2 methods: TIA (GCCL, Yongin, Korea) and Nep (GC Pharma, Yongin, Korea), and compared all values among the 3 groups to determine the effect of age and sex. Correlations between total IgG and the sum of each IgGSC as well as intraclass correlation coefficients (ICCs) in both methods were analyzed. The RIs each of Igs and IgGSCs were calculated in 2 ways (parametric RI: mean ± 2 standard deviation, nonparametric RI: 2.5th to 97.5th percentiles) after Box-Cox transformation and then re-tranformation. Statistical analysis was performed using GraphPad Prism, version 8.4.3 (GraphPad Software, Inc., La Jolla, CA, USA); SPSS, version 25 (IBM SPSS Statistics; IBM Corporation, Chicago, IL, USA) and R, version 4.0.0 (R Project for Statistical Computing, Vienna, Austria). A *P* value of <0.05 was considered significant.

Table summarizes mean levels, ICCs and the RI each of IgG/A/M and 4 IgGSCs as measured using Nep and TIA. IgM levels (measured using both methods) were higher in female subjects than in male counterparts (1.36 vs 1.06 g/L for Nep, $P < 0.001$; 1.40 vs 0.94 g/L for TIA, $P < 0.001$, **Supplementary Fig. S1**), which are comparable to the results of a previous study.[4] It is

Disclosure

There are no financial or other issues that might lead to conflict of interest.

known that 17-β estradiol may induce Ig production and stimulate humoral immunity.[5] Serum IgM levels were lower in subjects aged >60 years than in those aged <60 years, with significant differences in both methods ($P < 0.05$ and $P < 0.05$, respectively, **Supplementary Fig. S1**). Other Igs showed an inconsistent difference with no significance between the 2 methods in terms of sex and age, suggesting that sex and age could not affect serum IgG and IgGSC levels in our population (**Supplementary Fig. S2**).

Nep and TIA are major methods to measure IgGSC levels for the diagnosis of immunological disease. To determine the cutoff value each of IgGSCs, they were simultaneously measured and compared between the 2 methods. A significant correlation was noted between total IgG and sum of IgGSC levels ($r = 0.93$, $P < 0.05$ and $r = 0.93$, $P < 0.05$, respectively). The ICCs of IgG/IgA/IgM and 4 IgGSCs were over 0.8, showing good correlations between the 2 methods.

In Bland-Altman analysis, the mean bias of the TIA:Nep ratio of IgG/IgA/IgM/IgG1 and IgG2 showed nearly the same ratio with a relatively narrow range of 95% limit of agreement. The mean biases of the TIA:Nep ratios of IgG3 and IgG4 levels were found to be 1.93 and 0.72, respectively, with wide ranges of 95% limit of agreement (1.20-2.65 and 0.27-1.17), which were also comparable to the results of previous studies (**Supplementary Fig. S3**).[6,7] In our study, when upper and lower limits of RI each for IgG3 and IgG4 levels were compared to those of other cohorts reported in Central Europe and Korea as well as those provided by the manufacturer (30 healthy adult donors from Birmingham Blood Transfusion Service), they showed significant differences between the 2 methods as shown in **Supplementary Fig. S4**.[6] These findings suggest that it is ideal to adopt RIs using the same method to obtain consistent and reliable results for the diagnosis and monitoring of patients with IgG3SCD- or IgG4-related disease in clinical practice. Besides RI values, functional aspects of IgG response, such as specific IgG response to pneumococcus, are required for the diagnosis of humoral immunodeficiency patients with normal levels of RI.

Table. The levels of IgG, IgA, IgM and IgG subclasses, ICC and RIs measured using Nep and TIA (n = 200)

Ig subclasses (g/L)	Mean ± SD	95% CI for mean	Percentile					ICC	Parametric RIs	Nonparametric RIs
			Min	25%	Median	75%	Max			
IgG								0.93*		
Nep	12.33 ± 2.14	12.03–12.62	7.37	10.80	12.25	13.50	19.90		8.81–16.85	8.84–17.21
TIA	12.49 ± 2.21	12.18–12.80	7.36	10.80	12.53	13.78	19.58		8.59–17.09	8.66–17.41
IgA								0.96*		
Nep	2.39 ± 0.94	2.26–2.52	0.80	1.77	2.26	2.77	6.88		1.17–4.29	1.13–4.41
TIA	2.36 ± 0.99	2.22–2.49	0.69	1.66	2.20	2.86	6.76		0.99–4.64	1.01–4.60
IgM								0.90*		
Nep	1.21 ± 0.59	1.13–1.29	0.24	0.76	1.11	1.50	3.74		0.42–2.65	0.47–2.85
TIA	1.17 ± 0.61	1.08–1.25	0.21	0.75	1.01	1.43	4.39		0.40–2.58	0.43–2.53
IgG1								0.93*		
Nep	7.41 ± 1.56	7.19–7.62	4.02	6.35	7.22	8.24	14.10		4.97–10.76	4.96–10.71
TIA	6.89 ± 1.62	6.67–7.12	3.85	5.71	6.76	7.71	13.72		4.35–10.53	4.34–10.50
IgG2								0.93*		
Nep	4.21 ± 1.55	3.99–4.42	1.46	3.26	4.02	5.01	10.80		2.07–7.38	1.86–7.07
TIA	5.12 ± 1.56	4.91–5.34	2.01	4.07	4.92	6.32	10.27		2.43–8.53	2.21–8.54
IgG3								0.80*		
Nep	0.27 ± 0.17	0.24–0.29	0.05	0.14	0.22	0.35	0.94		0.06–0.73	0.07–0.69
TIA	0.50 ± 0.30	0.46–0.54	0.07	0.27	0.44	0.67	1.80		0.11–1.27	0.11–1.24
IgG4								0.88*		
Nep	0.58 ± 0.49	0.51–0.65	0.01	0.23	0.44	0.79	3.14		0.05–1.80	0.05–1.98
TIA	0.38 ± 0.30	0.34–0.43	0.01	0.18	0.30	0.51	1.97		0.05–1.07	0.06–1.21

IgG, immunoglobulin G; IgA, immunoglobulin A; IgM, immunoglobulin M; ICC, intraclass correlation; Nep, nephelometry; TIA, turbidimetric immunoassay; SD, standard deviation; CI, confidence interval; Min, minimum; Max, maximum; RIs, reference intervals.
*$P < 0.001$.

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In conclusion, the present study provides the RI each of Igs and IgGSCs in Korean healthy adults and suggests their cutoff values for the diagnosis of humoral immunological disease in adult patients.

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SUPPLEMENTARY MATERIALS

Supplementary Fig. S1

Comparisons of serum IgM according to sex and age as measured by TIA, Nep.

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Supplementary Fig. S2

Comparison serum Ig levels according to sex and age in IgA/IgG4 using Nep (A/B) and IgG2 using TIA (C). These figures show median values (solid lines), interquartile ranges (boxes), non-outlier ranges (whiskers), and outliers (circles).

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Supplementary Fig. S3

Comparison of serum levels each of Igs and IgGSCs between TIA and Nep analyzed by using Bland-Altman plots.

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Supplementary Fig. S4

Comparisons of RIs of IgG3 (A) and IgG4 (B) measured by Nep and TIA in 2 Korean cohort and manufacturers.

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