

IMMUNOGLOBULINS, IMMUNOGLOBULIN G SUBCLASSES AND COMPLEMENT IN ADULT OMANIS

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Immunoglobulins and complement were quantitated in 100 healthy adult Omanis in order to establish a reference range based on local data. Mean values were IgA 2.38 g/L, IgM 1.14 g/L, IgE 241 kiu/L, C3 7.44 μ mol/L and C4 1.57 μ mol/L, values similar to those found in the West. However, the mean level of IgG was almost 50% higher than that found in North America and Europe, that is, 14.63 g/L compared with 10-11 g/L. The values for IgG, IgA, IgM and IgE are similar to those reported for Iraq, but IgG levels were much lower than those found in Iran (25.52 g/L), although IgA, IgM and IgE were comparable. Comparison of Omani data with that for Saudi Arabia showed significantly more IgG in Oman (14.63 versus 11.68 g/L) and significantly less IgM (1.14 versus 1.66 g/L). IgA and IgE levels were similar. As reported elsewhere, females had significantly more IgM than males (1.32 versus 0.97 g/L). The levels of IgG subclasses in Oman are 9.44, 4.01, 1.06 and 0.62 g/L for IgG1-4 respectively. The percentage of the various subclasses are very similar to those reported elsewhere, that is, 62%, 27%, 7% and 4% for IgG1-4. However, in Iraq, a higher percentage (and level) of IgG3 (16%) and the lower IgG2 (18%) compared to Oman may reflect differing immune responses resulting from exposure to different microorganisms. It is essential to use local reference data when evaluating patients. *Ann Saudi Med 1997;17(1):39-42.*

When evaluating patients with recurrent infections, suspected immunodeficiency, allergic disease and many other conditions, it may be necessary to quantitate the levels of immunoglobulins. The values obtained are then compared with a so-called normal range. In many instances, these normal ranges are supplied by the manufacturer of the equipment or the reagents used in quantitation and may not reflect the normal values of the local population. There is no published information on the normal values of these "immunoproteins" in healthy adult Omanis and very little data on the Gulf Arabs in general.¹⁻⁵ Reports from elsewhere would indicate that there may be significant differences depending on race and environment.^{6,7}

We have studied 100 healthy adult Omanis (50 males/50 females) in order to obtain local reference values to be used when evaluating patients. We compare our findings with those in other populations.

Material and Methods

One hundred healthy Omanis over the age of 18 years,

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comprising 50 males and 50 females, were measured for the following immunoproteins: immunoglobulin classes G, A, M, E, subclasses IgG1, 2, 3 and 4 and complement proteins C3 and C4.

The population of Oman is comprised of three major ethnic groups originating in Arabia, Africa and Beluchistan. The Omanis included in the study are either students at Sultan Qaboos University, blood donors, or potentially healthy living donors of bone marrow or kidneys. None of the controls were related to each other and were considered to represent a cross-section of the Omani population.

Immunoglobulins G, A, and M and complement C3 and C4 were measured by nephelometry using the Beckman Array Analyzer (Beckman Instruments, Inc., California, USA). Immunoglobulin E was assayed using the Abbott IMx analyzer, using the principle of microparticle enzyme immunoassay (Abbott Labs, Illinois, USA).

The subclasses of IgG were estimated by single radial immunodiffusion using an IgG subclass combikit (ref. CUS0045SD, Serotec, Oxford, UK). All assays included manufacturers reference/calibration standards for comparison with the Omani samples. The results were analyzed and expressed in terms of mean, median, standard deviation, 95% confidence intervals (of the mean) and maximum and minimum values. All the results were

TABLE 1. Immunoglobulin and complement levels in adult Omanis.

	IgG g/L	IgA g/L	IgM g/L	IgE kiu/L	IgE kiu/L*	C3 μ mol/L	C4 μ mol/L
No.	100	100	100	100	75	100	100
Mean	14.63	2.38	1.14	241**	76	7.44	1.57
Standard deviation	2.52	0.84	0.50	406	62	1.86	0.52
Median	14.25	2.25	1.09	81	62	7.10	1.51
Minimum	9.60	0.67	0.32	3	3	4.80	0.71
Maximum	21.60	4.78	3.04	2651	294	13.60	3.07
95% confidence interval about mean	14.13-15.13	2.21-2.54	1.05-1.24	161-321	61-90	7.10-7.80	1.46-1.67

*Excluding potentially allergic individuals with total IgE>300 kiu/L; **as IgE is not normally distributed, the mean and standard deviation are not appropriate. The mean, the range and the 2.5-97.5 percentile (4-1398 kiu/L) are relevant.

TABLE 2. Immunoglobulin G subclass levels in adult Omanis.

	IgG1 g/L	IgG2 g/L	IgG3 g/L	IgG4 g/L	Total IgG subclasses
No.	100	100	100	100	75
Mean	9.44	4.01	1.06	0.62	15.13
Standard deviation	2.21	1.37	0.42	0.41	2.91
Median	9.08	4.16	1.02	0.58	14.74
Minimum	4.19	1.17	0.21	0.00*	--**
Maximum	14.35	7.79	2.32	1.76	--
95% confidence interval about mean	9.0-9.87	3.74-4.29	0.97-1.14	0.54-0.70	--
% of total subclasses	62%	27%	7%	4%	100%

*1 individual IgG4 deficient; **not applicable when totalling subclasses.

examined to see if they approximated to a normal distribution. If they were not normally distributed, the data is given in terms of the median and the 2.5 to 97.5 percentiles. Comparison between means was calculated using the standard error of the difference between means and referring to probabilities estimated from multiples of the standard error in relation to a normal distribution.⁸

Results

The results for immunoglobulin classes and complement are shown in Table 1 and for the subclasses of IgG are shown in Table 2. All of the parameters measured, except IgE, approximated a normal distribution. A normal probability plot and a frequency histogram for IgE revealed significant skewing. The 2.5 to 97.5 percentiles for IgE are included in Table 1, in addition to the mean and standard deviation, to enable comparison with other published data.

In view of the fact that in a normal population of 100 individuals, a significant proportion are likely to be allergic, two sets of data for IgE are given. The first set includes all the controls and the second set those with values less than 300 kiu/L, since those with values higher than this may be allergic or parasitized. Data from the United Kingdom indicate that approximately 40% of the population with an IgE level of between 200 and 450 kiu/L are atopic.⁹ Although all the individuals in this study were questioned on their health, none indicated that they were allergic. A cut-off value of 300 kiu/L was considered to be acceptable to distinguish between those who were normal and those who were potentially allergic.

The correlation coefficient between the sum of the individual subclasses added together (measured by RID) and the total IgG measured independently by nephelometry was 0.83 and the respective means were a total IgG 14.63 g/L (SD=2.53) and the sum of the IgG subclasses 15.13 g/L (SD=2.91). This difference is not significant ($P>0.1$).

Figure 1 compares the immunoglobulin data for the 50 males and 50 females in the survey. There were no differences in complement components C3 and C4 between males and females. Females had a tendency to have higher IgG levels than males, the former being due to higher levels of IgG1 and IgG2. IgG3 was similar in both sexes and IgG4 and IgE were higher in males, although none of these differences were significant. However, females did have significantly more IgM than males, 1.32 versus 0.97 g/L ($P<0.001$).

Discussion

Immunoglobulin levels are influenced by age, sex, race and environment. Different environments present different antigens to the individual and these will determine the immunoglobulin levels in the individual. Thus it is expected that populations exposed to different environments will have different immunoglobulin levels

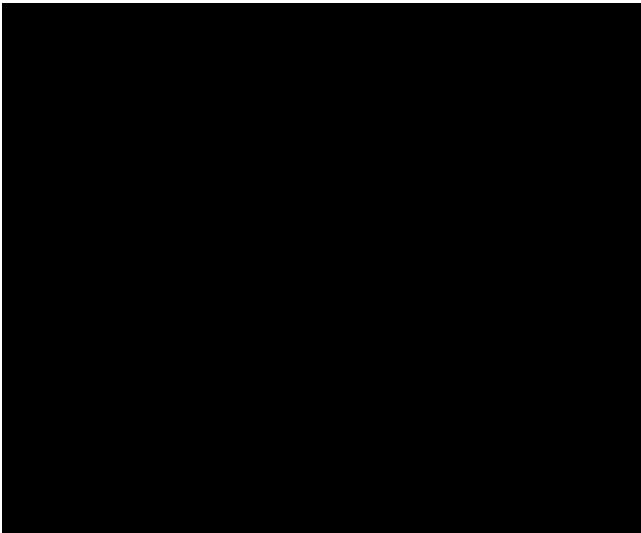


FIGURE 1. Comparison of immunoglobulin levels in 50 adult Omani males and 50 females.

and hence, a reference range has to be generated for each population. Measurement of gammaglobulin levels may provide a useful measure of the ecological stress resulting from infections to which the population is subjected.⁴

Two studies by the same author on Iraqis carried out in 1977 and 1982 revealed very disparate results for IgG levels.^{1,2} The IgG levels reported in 1977 were 8.22 g/L and in 1982 were 15.66 g/L. In fact, values for all the immunoglobulins reported in 1977 were lower than those in 1982. The values obtained in 1982 are slightly higher but comparable to those obtained by us in Omanis for IgG, IgA, IgM and IgE. However, in another study of IgG subclasses in Iraq,³ the total IgG level was reported as 9.95 g/L. Comparison with data obtained in Saudi Arabia⁵ showed significantly higher levels of IgG in Oman (14.63 versus 11.67 g/L, $P < 0.001$), significantly lower levels of IgM (1.14 versus 1.66 g/L, $P < 0.01$) and similar levels of IgA and IgE (potentially atopic excluded).

A study carried out in Iran in 1987⁴ found comparable levels of IgA (2.48 versus 2.38 g/L) and IgE (259 versus 241 kiu/L) with Oman but significantly different values for IgG (25.52 versus 14.63 g/L, $P < 0.001$) and IgM (1.79 versus 1.14 g/L, $P < 0.001$). The authors examined various subpopulations and noted higher IgG, IgA and IgE levels in rural compared with urban dwellers. They also commented that IgG levels resembled those found in Africa rather than in Europe. An African study¹⁰ comparing urban with rural dwellers found significantly higher IgA and IgG, but lower IgM in the urban dwellers compared with the rural population. The IgG value for the urban and rural populations combined was 19.4 g/L. They concluded that different patterns of parasitic infestation in the two populations may be important.

The IgG values for Iran and Africa are much higher than those reported in the West. American adults have a mean IgG value of 10.05 g/L and Germans 11.00 g/L.¹¹ Omanis fall in between Africa and the West with a mean value of 14.63 g/L. Thus, the mean IgG levels in Oman are approximately 50% higher than the mean value for IgG in the West ($P < 0.001$). The values for IgA, IgM and IgE are comparable to those found in Americans and Germans. The values for complements C3 and C4 are also similar to those found in the West.¹¹ Our data also confirm the significant difference in IgM concentration between males and females 0.97 and 1.32 g/L respectively ($P < 0.001$). Saudi Arabian females have more IgM than males (1.96 versus 1.38 g/L $P < 0.002$),⁵ American males 1.36 g/L, American females 1.70 g/L, German males 1.13 g/L and females 1.47 g/L.¹¹

There is little information on immunoglobulin G subclasses in the Gulf populations. Shakib et al.³ have reported IgG subclass values in Iraqi Arabs. Their values are significantly different ($P < 0.001$) to those found in Oman, specifically IgG1 = 9.44 g/L (Oman) versus 5.92 g/L (Iraq), IgG2 = 4.01 versus 1.72, IgG3 = 1.06 versus 1.45, and IgG4 = 0.62 versus 0.25 g/L. Omanis have similar percentages of the various subclasses to those reported elsewhere,³ that is 62%, 27%, 7% and 4% for IgG1-4 respectively. Iraqi Arabs have a marked elevation of IgG3 (% and level) and a reduction of IgG2 when compared to findings in Caucasian populations. In Omanis, the IgG3 level approaches Caucasian levels and IgG2 is a higher percentage and level than in Iraqis. This difference in IgG3 and IgG2 percentage and levels may reflect the differing immune response to different microorganisms. It is known that IgG2 provides the dominant response to polysaccharide antigens (e.g., *Streptococcus pneumoniae* and *Haemophilus influenzae*) and IgG3 to protein and polypeptide antigens.⁷ No other values for IgG subclasses are available on the Gulf Arabs. An Egyptian study on schistosomiasis reports control values of IgG1 of 7.02 g/L, IgG2 of 1.95 g/L, IgG3 of 0.37 g/L and IgG4 of 0.34 g/L,¹² values lower than those found in Oman. A recent study in Turkey¹³ reported IgG1 levels as 6.62 g/L, IgG2 as 3.77 g/L, IgG3 as 0.70 g/L, and no values were given for IgG4. Thus, Omanis have higher levels of all subclasses.

The total of the subclasses was well correlated with the total IgG ($r = 0.83$), supporting the accuracy of our findings. A study carried out in Italy reported a correlation of 0.77 between the sum of the subclasses and the concentration of total IgG.¹⁴ However, the values for total IgG were, in general, higher than those for the total of the subclasses, whereas our findings showed slightly higher total subclasses than total IgG (15.13 versus 14.63 g/L). This difference is not significant and probably reflects the

comparison between a single measurement by nephelometry to determine total IgG compared to the addition of four measurements of diameters using radial immunodiffusion to quantitate each IgG subclass. In view of these findings, it is apparent that reference ranges should always be generated from local data when examining a patient's results.

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References

1. Al Agidi SK, Papiha SS, Roberts DF. Immunoglobulin levels in Iraq. *Clin Exper Immunol* 1977;29:247-55.
2. Al Agidi SK, Shukri SM. Association between immunoglobulin levels and known genetic markers in an Iraqi population. *Ann Human Biol* 1982;9:565-9.
3. Shakib F, James K, Barr D. Gm allotypes and IgG subclasses in Iraqi Arabs. *J Immunogenetics* 1982;9:149-53.
4. Papiha SS, Roberts DF, Behjati F, Akbari M. Genetic and environmental factors affecting immunoglobulin levels in Iran. *Z Morph Anthropol* 1987;77:143-55.
5. Harfi HA, Godwin JT. Normal serum levels of IgG, IgA, IgM, IgD, and IgE in Saudi Arabia. *King Faisal Specialist Hosp Med J* 1985;5:99-105.
6. Geller-Bernstein C, Kennet R, Barsky T, Tsur S, Lahav M, Levin S. IgA, IgG, IgM and IgE levels in normal healthy, nonatopic Israeli children. *Ann Allergy* 1988;61:296-9.
7. Bradwell AR. IgG subclasses in Disease. 3rd edition. Birmingham, UK: The Binding Site, Ltd, 1993.
8. Swinscow TDV. Differences between means. In: *Statistics at Square One*. London: Br Med Assoc, 1990:28-30.
9. Roitt I, Brostoff J, Male D. Hypersensitivity - Type 1. Chapter 19. In: *Immunology*, 3rd edition. London: Mosby Year Book Ltd, 1993;19:4.
10. Mohammed I, Tomkins AM, Greenwood BM. Normal immunoglobulins in the tropics. *Lancet* 1973;1:481.
11. Lentner C, editor. Geigy Scientific Tables, Vol 3. In: *Physical Chemistry, Components of the blood, hematology, somatometric data*, 8th ed. Basel: Ciba Geigy, 1984;149-56.
12. Boctor F, Peter JB. IgG subclasses in human chronic schistosomiasis: overproduction of schistosome-specific and nonspecific IgG4. *Clin Exp Immunol* 1990;82:574-8.
13. Berkel AI, Teczan I, Ersoy F, Sanal O. Serum immunoglobulin G subclass values in healthy Turkish children and adults. *Turk J Paediatr* 1994;36:197-204.
14. Plebani A, Ugazio AG, Avanzini MA, Massimi P, Zonta L, Monafò V, Burgio GR. Serum IgG subclass concentrations in healthy subjects at different ages: age normal percentile charts. *Eur J Pediatr* 1989;149:164-7.