ON THE NATURE OF CORRELATION BETWEEN PLASMA PROTEINS

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SUMMARY: This study was conducted to determine the nature of correlation between plasma proteins in healthy individuals. Blood samples were collected from children, male and female adults, and using rate nephelometry plasma albumin, transferrin, α1-antitrypsin, group specific component (Gc protein) and three immunoglobulins, IgG, IgM, and IgA were estimated in each sample. Each protein was subjected to regression analysis with each of the other proteins and correlation coefficients were determined.

A statistically significant ($p<0.007$) positive correlation was obtained between each of the proteins in the children, except between Gc protein and the other six plasma proteins investigated. While in adults the results were different for IgA and IgM when compared with those for the children.

In this paper we present the results of regression analysis and correlation coefficients between seven plasma proteins in children and adults and discuss their possible causes and significance.

Key Words: Albumin, Transferring, α1-Antitrypsin, Gc, Immunoglobulins.

INTRODUCTION

Human plasma contains over a 100 different types of proteins, several with important biological functions and of physiological and medical significance, particularly as transient indicators of disease, tissue damage and cellular changes (1).

A few studies have reported correlations between the level of albumin and some of the other plasma proteins. A positive correlation was reported between albumin and transferrin, while a negative correlation was reported between albumin and the immunoglobulins (2-4), and the acute phase proteins (5), in certain disease states.

Since correlations between several of the plasma proteins in normal healthy male and female adults and children are not clear, we initiated this study to determine, firstly the nature of correlation between plasma levels of seven plasma proteins and secondally, to investigate the effect of age and sex on these correlations.

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In this paper the results of regression analysis and correlation coefficients between seven plasma proteins are presented and the possible causes and significance of these results are discussed.

MATERIALS AND METHODS

The subjects investigated were 1165 apparently healthy Saudi males, females and children (265, 312 and 588 respectively). Medical examination was carried out and history were taken by a clinician. Blood samples were collected in heparinized tubes and plasma was separated from the cells by centrifugation. The plasma was stored at -20°C until required for analysis. The plasma proteins ie albumin, transferrin α1-antitrypsin, group specific component protein (Gc), IgG, IgM, and IgA were estimated using a Rate Nephelometric System (Beckman Instruments Inc., Brea CA). Special kits for each protein, except Gc, were obtained from Beckman Inc., and the estimation was carried out using the procedure provided by the manufacturer. Rabbit antihuman Gc globulin was obtained from dako (Denmark). A normal control serum with known concentration of each protein was included with each set of assays and wherever possible the samples were analyzed in duplicates.

Table 1: The correlation coefficient (R) and P value for different plasma proteins in children.

Correlation between		IgG	IgA	IgM	Alb	Gc	Trf	AAT
IgG	R	-	0.383	0.309	0.383	0.0814	0.436	0.353
	P		0.0001	0.0001	0.0001	0.0671	0.0001	0.0001
	(No)		(588)	(588)	(587)	(507)	(588)	(585)
IgA	R	0.383	-	0.2100	0.188	0.067	0.305	0.289
	P	0.0001	-	0.0001	0.0001	0.134	0.0001	0.0001
	(No)	(588)	-	(588)	(587)	(506)	(588)	(585)
IgM	R	309	0.210	-	0.148	0.049	0.265	0.289
	P	0.0001	0.0001	-	0.0003	0.263	0.0001	0.0001
	(No)	(588)	(588)	-	(587)	(507)	(588)	(585)
Alb	R	0.383	0.188	0.148	-	-0.013	0.576	0.353
	P	0.0001	0.0001	0.0001	-	0.762	0.0001	0.0001
	(No)	(587)	(587)	(587)	-	(528)	(587)	(584)
Gc	R	0.081	0.069	0.049	-0.013	-	0.055	-0.051
	P	0.0671	0.1336	0.263	0.7622	-	0.214	0.2566
	(No)	(507)	(506)	(507)	(528)	-	(506)	(503)
Trf	R	0.436	0.305	0.265	0.576	0.055	-	0.387
	P	0.0001	0.0001	0.0001	0.0001	0.214	-	0.0001
	(No)	(588)	(588)	(588)	(587)	(506)	-	(586)
AAT	R	0.0353	0.289	0.289	0.353	-0.051	0.387	-
	P	0.0001	0.0001	0.0001	0.0001	0.256	0.0001	-
	(No)	(585)	(585)	(585)	(584)	(503)	(586)	-

Alb = Albumin, Gc = Group specific component, Trf = Transferrin, AAT = α1-antitrypsin, (No) = No. of samples investigated

RESULTS

The results obtained for each protein as mg/dl, were fed on the computer at the computer center, King Saud University, Riyadh, and using the General Linear model (GLMN) program of "Statistical Analysis System" (SAS) regression analysis was carried out and Correlation coefficients (R) were determined between each protein. The statistical significance of the correlation was obtained using the students 't' test. $P<0.05$ was considered statistically significant. The samples from children (<15 years) and male and female adults were analyzed separately. Tables 1, 2, 3 present the correlation coefficient (R) and the P value obtained following regression analysis between the various proteins in children, adult males and females respectively. Among the children, a statistically significant positive correlation was obtained between each of the plasma proteins except between Gc protein and the other 6 plasma proteins investigated (Table 1).

In the adult group no significant correlation was obtained between the Gc protein and the other six proteins in the male population, however, in the female IgG and albumin correlated significantly with Gc protein. IgG correlated positively with IgA, IgM, albumin, transferrin and α1-antitripsin both in the males and in the females. IgA correlated positively with IgG and IgM, but not with albumin and transferrin both in the male and female group. In addition, with α1-antitrypsin a positive correlation was obtained in the male but not in the female. IgM showed a statistically significant positive correlation with albumin, transferrin and α1-antitrypsin in the male population, but not in the female population. Albumin correlated positively with transferrin in the male and no correlation was obtained with α1-antitrypsin. On the other hand between albumin and both transferrin and α-antitrypsin a statistically significant negative correlation was obtained in the females, while transferrin correlated positively with α1-antitrypsin both in the male and female adults.

In addition, the sample's from males, females and children were also grouped together and analyzed, to determine whether any correlation could be demonstrated between the various proteins. The intercept, slope, correlation coefficient (R) and the P value are presented in Table 4. In the total group IgG correlated positively with IgA, IgM, albumin, transferrin and α1-antitrypsin, but not with albumin and Gc protein. Albumin showed a statistically significant positive correlation both with transferrin and α1-antitrypsin. Finally a statistically significant positive correlation was obtained between transferrin and α1-antitrypsin level.

Table 2: Correlation coefficient (R) and P value between different plasma proteins in adult male group.

Correlation between		IgG	IgA	IgM	Alb	Gc	Trf	AAT
IgG	R	-	0.333	0.185	0.225	-0.090	0.295	0.297
	P	-	0.0001	0.0047	0.0005	0.178	0.0001	0.0001
	(No)	-	(243)	(232)	(238)	(265)	(243)	(220)
IgA	R	0.333	-	0.207	0.107	0.043	0.077	0.224
	P	0.0001	-	0.0014	0.097	0.5156	0.2303	0.0008
	(No)	(243)	-	(233)	(239)	(226)	(244)	(221)
IgM	R	0.185	0.207	-	-0.158	0.099	0.255	0.482
	P	0.0047	0.0014	-	0.017	0.1450	0.0001	0.0001
	(No)	(232)	(233)	-	(229)	(215)	(233)	(210)
Alb	R	0.225	0.107	-0.1577	-	0.049	0.145	-0.0425
	P	0.0005	0.0974	0.0167	-	0.3186	0.0247	0.5329
	(No)	(238)	(239)	(229)	-	(265)	(240)	(217)
Gc	R	-0.0901	0.043	0.099	0.0496	-	0.037	0.091
	P	0.178	0.515	0.145	0.3186	-	0.5766	0.1956
	(No)	(225)	(226)	(215)	(265)	-	(227)	(204)
Trf	R	0.295	0.0771	0.255	0.145	0.037	-	0.351
	P	0.0001	0.230	0.0001	0.0247	0.576	-	0.0001
	(No)	(243)	(244)	(233)	(240)	(227)	-	(222)
AAT	R	0.297	0.225	0.482	-0.042	0.019	0.351	-
	P	0.0001	0.0008	0.0001	0.5329	0.1956	0.0001	-
	(No)	(220)	(221)	(210)	(217)	(204)	(222)	-

Alb = Albumin, Gc = Group specific component, Trf = Transferrin, AAT = α1-antitrypsin, (No) = No. of samples investigated.

Table 3: Correlation coefficient (R) and P value for different proteins in adult female group.

Correlation between		IgG	IgA	IgM	Alb	Gc	Trf	AAT
IgG	R	-	0.355	0.222	0.245	0.142	0.110	0.091
	P	-	0.0001	0.0001	0.0001	0.021	0.050	0.109
	(No)	-	(312)	(297)	(304)	(266)	(312)	(310)
IgA	R	0.355	-	0.357	0.006	0.004	0.052	0.037
	P	0.0001	-	0.0001	0.9111	0.943	0.359	0.516
	(No)	(312)	-	(297)	(303)	(265)	(312)	(310)
IgM	R	0.222	0.357	-	0.034	-0.041	0.1117	0.059
	P	0.0001	0.0001	-	0.566	0.824	0.054	0.305
	(No)	(297)	(297)	-	(289)	(250)	(297)	(295)
Alb	R	0.245	0.006	0.034	-	0.119	-0.157	-0.395
	P	0.0001	0.911	0.566	-	0.021	0.006	0.0001
	(No)	(304)	(303)	(287)	-	(372)	(303)	(301)
Gc	R	0.141	0.004	-0.014	0.119	-	0.107	-0.007
	P	0.020	0.943	0.824	0.021	-	0.080	0.912
	(No)	(266)	(265)	(250)	(372)	-	(265)	(263)
Trf	R	0.11	0.052	0.111	-0.157	0.107	-	0.644
	P	0.050	0.359	0.054	0.006	0.080	-	0.0001
	(No)	(312)	(312)	(297)	(303)	(265)	-	(301)
AAT	R	0.091	0.037	0.059	-0.395	-0.007	0.644	-
	P	0.109	0.516	0.305	0.0001	0.912	0.0001	-
	(No)	(310)	(310)	(295	(301)	(263)	(310)	-

Alb = Albumin, Gc = Group specific component, Trf = Transferrin, AAT = α1-antitrypsin, (No) = No. of samples investigated

DISCUSSION

This study has shown that significant correlations exist between some of the plasma proteins while not between others in healthy male and female adults and children. This study also showed that both sex and age have an influence on the correlation between some proteins, while not on others. All three immunoglobulins correlated positively with each other and the correlation was statistically significant irrespective of the age or sex in healthy individuals. Thus an increase in IgG was accompanied by an increase in IgM and IgA level, though the values remained within the normal range (6). These results are in agreement with results of a study on patients with generalized infection, in whom it was shown that the percentage increase in IgG, IgM and IgA was similar (7,8).

An interesting result was a positive correlation between the levels of albumin and IgG, irrespective of age and sex. On the other hand albumin level correlated positively with IgA and IgM level in the children, but no correlation was seen in adults. This was contradictory to the results reported earlier when it was shown that in hot tropical climates, albumin levels were depressed often in association with elevation of the γ-globulin fraction (2,3) and this decrease in albumin was believed to be secondary to the elevation in γ-globulin level (4). In normal healthy individuals, the results of our study can be explained on the basis of the compensatory mechanism in the human body which help to keep the albumin/globulin ratio constant. This would explain that as albumin is increased or decreased, a corresponding change also occurs in the level of globulins thus resulting in a stable A/g ratio. In disease states, however, the situation is generally altered. In liver or renal diseases albumin is usually decreased due to decreased production or increased excretion of albumin while globulins may be normal, thus the A/G ratio is decreased (1). On the other hand, infections cause an increase in the globulin level keeping albumin constant and therefore decrease the A/G ratio (1).

Another interesting result in our study was the correlation between albumin and transferrin which was positive in the children and the male group but negative in the

Table 4: Correlation coefficient (R) intercept, slope and P value for different plasma proteins.

	Intercept	Slope	R	P
Correlation between				
IgG and IgA	1002.98	1.23	0.375	0.0001
IgM	1080.52	1.53	0.275	0.0001
Alb	688.3	0.139	0.282	0.0001
Gc	1122.09	3.898	0.0980	0.0019
Trf	913.275	1.052	0.284	0.0001
AAT	1045.28	1.193	0.247	0.0001
Correlotion between				
IgA and IgM	145.82	0.158	0.305	0.0001
Alb	143.993	0.015	0.1	0.0007
Gc	175.167	1.0715	0.088	0.0050
Trf	136.6	0.214	0.189	0.0001
AAT	144.5	0.3395	0.23	0.0001
Correlation between				
IgM and Alb	111.85	0.001	0.013	0.663
Gc	93.55	0.703	0.10	0.0015
Trf	60.87	0.172	0.253	0.0001
AAT	69.32	0.262	0.303	0.0001
Correlation between				
Alb and Gc	4035.95	2.43	0.0283	0.2861
Trf	3736.75	1.12	0.148	0.0001
AAT	4258.06	-0.845	0.084	0.005
Correlation between				
Trf and AAT	199.887	0.710	0.5495	0.0001

female group. Variation in the transferrin level in the male and female population have been previously encountered (9) and it is possible that the different requirement for iron in the two sexes influence the transferrin level. Since both albumin and transferrin are synthesized in the liver, any condition resulting in decrease in albumin level may also result in decrease in albumin level may also result in decrease in the transferrin level thus producing a positive correlation. In a study recently reported, a positive correlation was obtained between albumin and transferrin level in patients suffering from nephrotic syndrome (10). Also in patients with stress due to extreme shock both albumin and transferrin levels are reported decrease (5). In healthy individuals, like those in our study, the correlation may be explained by assuming that this is an attempt of the body to keep an equal ratio of the various plasma proteins.

The results of our study also showed a statistically significant positive correlation between transferrin and the immunoglobulins. It has been shown in an earlier study that in patients with nephrotic syndrome a similar correlation exists (10). It has also been suggested that serum transferrin level influences the immunoglobulin synthesis by effecting the lymphocyte proliferation. Thus in patients with hypotransferrinemia, the immunoglobulin level is decreased while an increase in trasferrin level is accompanied by an increase in immunoglobulin level (10).

α1-antitrypsin also correlated significantly with the levels of immunoglobulins and except in the female, the correlation was positive and statistically significant in children and adult males. The cause for this difference in the male and female results is not clear. α1-antitrypsin and transferrin correlated positively in children and adults (male and female) and the correlation was statistically significant. Both these proteins are synthesized in the liver and a specific ratio between α1-antitrypsin/transferrin is used as an indicator of the normal state and a decrease is reported to occur in individuals who suffer from α1-antitrypin deficiency (11,12). Thus in normal situation an increase in α1-antitrypsin should be accompanied by an increase in the transferrin level as shown in our study.

Gc protein did not show correlation with the other proteins investigated except with IgG and albumin in the female group only. Gc protein has been shown to be involved in transport of Vitamin D in the body. The normal range is reported to vary in the male and female population (Sedrani and Warsy, submitted for publication) and impossibly influenced by female hormonal status.

In conclusion, this study on healthy individuals has shown that a kind of homeostasis exists between majority of the plasma proteins and the ratio between the various proteins generally remains constant. It is the alterations in the normal ratios between the various proteins which is an indicator of a disease state and thus of importance in the differential diagnosis of a disease state.

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