

Deficiency of serum "pregnancy-associated" α_2 -glycoprotein (α_2 -PAG): association with disease

CHW HORNE,* LINDA M GERRIE,* SYLVIA S ARMSTRONG,* PW BRUNT,†
NAG MOWAT,† TS SINCLAIR†

From the *Department of Pathology, University Medical Buildings, Foresterhill, Aberdeen, and the †Gastrointestinal Unit, Woodend Hospital, Aberdeen, Scotland

SUMMARY The serum concentrations of "pregnancy-associated" α_2 -glycoprotein (α_2 -PAG) were measured in 129 healthy women and 141 healthy men to establish a normal range, using a sensitive enzyme linked immunosorbent assay. In the normal population 2.8% of men and 5.4% of women had low serum α_2 -PAG concentrations. Low concentrations occur, however, much more commonly in patients, particularly male patients, with certain diseases, including dermatitis herpetiformis (three of 12 or 25%) and urticaria (two of five or 40%). One female patient with absolute deficiency was also identified. In view of the recently confirmed association of α_2 -PAG with IgA and the fact that α_2 -PAG seems to have immunosuppressive properties, it seems likely that deficiency of α_2 -PAG could result in the subject becoming sensitised to various dietary antigens. Interestingly, none of the 24 patients with IgA deficiency showed concomitant deficiency of α_2 -PAG.

Alpha₂-glycoprotein associated with pregnancy (α_2 -PAG) is a serum glycoprotein of high molecular weight (360 000 daltons):^{1 2} it is present in all normal sera but usually only in relatively small amounts.^{3 4} Factors such as age and sex influence considerably the serum concentrations,⁵ and there is a striking rise during pregnancy⁶ and after the administration of oestrogens.^{7 8}

In recent immunolocalisation studies^{9 10} we showed that α_2 -PAG was present in most plasma cells that produce IgA within the lamina propria of the bowel. It is also detectable in other tissues with a preponderance of these cells—for example, lactating breast and salivary gland. Although the biological role of α_2 -PAG is not well defined, evidence suggests that it has immunosuppressive properties both in vivo and in vitro.¹¹⁻¹³ In view of this observation and because of its association with IgA we speculated as to whether α_2 -PAG may be an additional factor in the regulation of gut mucosal immunity. If α_2 -PAG does have a role in mucosal immunity it is not unrealistic to suppose that, as IgA deficiency is a relatively common disorder,^{14 15} α_2 -PAG deficiency may also occur. Indeed, a deficiency of IgA may occur concomitantly with a deficiency of α_2 -PAG.

Using a sensitive enzyme linked immunosorbent assay¹⁶ we measured α_2 -PAG concentrations in sera

from patients with IgA deficiency, from patients with various forms of gastrointestinal disease, and from those with other related conditions.

Material and methods

To establish a normal range of serum α_2 -PAG concentrations samples were obtained from 270 healthy adults (129 women, 141 men). All samples were stored at -20°C before assay.

A total of 24 samples from IgA deficient subjects were obtained from the department of chemical pathology, Foresterhill, Aberdeen; Dr Anne Ferguson, Edinburgh; Dr AG Bird, immunology unit, Newcastle General Hospital; and Dr A Milford-Ward, department of immunology, Royal Hallamshire Hospital, Sheffield.

One hundred and thirty nine samples from patients with other intestinal or related diseases were obtained mainly from inpatients and outpatients at Woodend General Hospital, Aberdeen. Additional samples were provided by Dr Anne Ferguson, gastrointestinal unit, Western General Hospital, Edinburgh, and by Dr V Alun Jones, Addenbrooke's Hospital, Cambridge. Table 1 shows the diseases studied and the number of patients in each category. Irritable bowel syndrome was diagnosed by exclusion of all other possibilities.

Alpha₂-PAG concentrations in sera were measured using an expanded enzyme linked immunoassay, as

Table 1 No of patients in each disease category studied (figures in parentheses show number of α_2 -PAG deficient subjects in each group)

Disease	Total No of patients	Male patients	Female patients
Irritable bowel syndrome	77 (5)	36 (5)	41
Coeliac disease	31 (2)	17 (2)	14
Dermatitis herpetiformis	18 (4)	12 (3)	6 (1)
Urticaria	12 (2)	5 (2)	7
Undiagnosed intestinal disorder	1 (1)		1 (1)
Totals	139 (14)	70 (12)	69 (2)

Table 2 Mean (SD) serum α_2 -PAG concentrations in IgA deficient (serum concentration $<0.4 \mu\text{g/l}$) subjects

No of subjects	Mean age (years) and (range)	Mean (SD) α_2 -PAG concentration ($\mu\text{g/l}$) and (range)
13 M	27.8 (6-57)	3890 (4420) (375-16275)
11 F	46.2 (13-76)	22410 (18690) (1590-66000)

described previously (unpublished observations). The lower sensitivity limit of the assay was $1 \mu\text{g/l}$.

Using a statistical computer package, the distribution of individual samples was plotted and linear regression analysis undertaken.

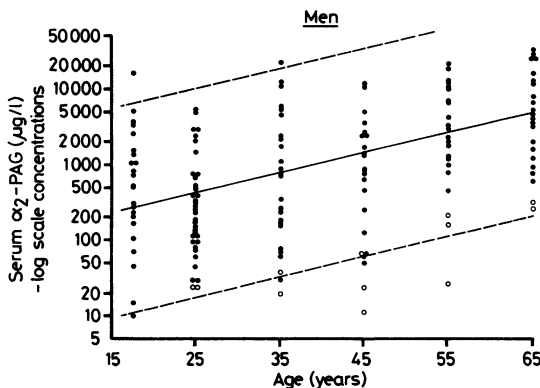


Fig. 1 Serum α_2 -PAG concentrations in men showing individual serum α_2 -PAG concentrations at each decade in healthy men (\bullet) and men with disease (\circ). Regression line and 95% confidence limits are indicated.

Results

Table 2 shows the mean serum concentrations and range of α_2 -PAG concentrations in men and women with IgA deficiency. None of these patients had concomitant deficiency of α_2 -PAG, but interestingly, the mean serum α_2 -PAG concentration in the 13 men with IgA deficiency was almost double that for normal subjects of the same age and sex (3890 $\mu\text{g/l}$ compared with 2080 $\mu\text{g/l}$). The 11 women with IgA deficiency had a mean α_2 -PAG concentration comparable with that of normal subjects (22410 $\mu\text{g/l}$ compared with 20170 $\mu\text{g/l}$).

Figs. 1 and 2 show the individual serum α_2 -PAG concentrations of 141 normal men and 129 normal women. Four (2.8%) men and seven (5.4%) women

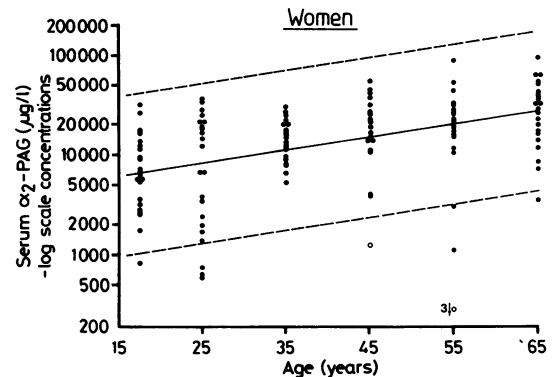


Fig. 2 Serum α_2 -PAG concentrations in women showing those of healthy women (\bullet) and women with disease (\circ). Regression line and 95% confidence limits are shown.

Table 3 Bowel disorders associated with deficiency of serum α_2 -PAG

Age (years) and sex	Serum α_2 -PAG ($\mu\text{g/l}$ *)	Clinical diagnosis
1 22 M	25 (845)	Irritable bowel syndrome
2 28 M	25 (845)	
3 30 M	30 (3225)	
4 31 M	20 (3225)	Food intolerance to corn and tomatoes
5 51 M	140 (6570)	Irritable bowel syndrome
6 51 F	<3 (24865)	
7 55 M	25 (6570)	Patient died of respiratory failure and intractable diarrhoea
8 60 M	250 (9670)	Untreated coeliac disease
		Coeliac disease

*Values in parentheses represent mean normal serum α_2 -PAG concentration for age group.

Table 4 Other conditions associated with deficiency of serum α_2 -PAG

Age (years) and sex	Serum α_2 -PAG ($\mu\text{g/l}^*$)	Clinical diagnosis
1 41 M	10 (4565)	Dermatitis herpetiformis
2 41 F	1175 (22650)	
3 58 M	180 (6570)	
4 71 M	200 (9670)	
5 42 M	50 (4565)	
6 45 M	25 (4565)	Urticaria

*Values in parentheses represent mean serum α_2 -PAG concentration for age group.

had concentrations that fell below the 95% prediction limits and were therefore classified as deficient.

A total of 139 patients suffering from the diseases listed in Table 1 were studied. Of these, a total of 14 (10.0%) showed α_2 -PAG deficiency, 12 of 70 men (17.1%) and two of 69 women (2.9%). Figs 1 and 2 show the exact α_2 -PAG concentrations in these deficient subjects, and Tables 3 and 4 give the clinical details for each patient and compare their serum α_2 -PAG concentrations with the mean for normal subjects of the same age and sex.

Using the data shown in Table 1 the percentage of deficient subjects within each disease category was: irritable bowel syndrome (6.5%); coeliac disease (6.5%); dermatitis herpetiformis (22.2%); and urticaria (16.7%). Considering only the male patients, however, the percentages were: irritable bowel syndrome (13.9%); coeliac disease (11.8%); dermatitis herpetiformis (25%); and urticaria (40%).

One patient (Table 3, case 6) had a serum α_2 -PAG concentration below that of the detection limit of the assay. This woman was suffering from, among other things, intractable diarrhoea and died three days after the blood sample was received.

Discussion

IgA deficiency is a relatively common disorder,¹⁶ but only a proportion of the affected subjects have associated gastrointestinal disease. This suggests that other factors prevent disease in such subjects. Could α_2 -PAG be one such factor? Although IgA and α_2 -PAG seem to be synthesised by the same plasma cells,⁹ we found no evidence for combined deficiency of the two proteins. On the contrary, we detected a trend towards increased serum α_2 -PAG concentrations in men with IgA deficiency. We shall continue to measure samples from such subjects to determine whether this is clinically important. No such trend was observed in women in whom a compensatory increase in α_2 -PAG may be unnecessary because of their higher endogenous concentrations of the protein (Figs. 1 and 2).

One of the most striking features of the data pertaining to α_2 -PAG deficiency (Table 1) is the substantially increased percentage of deficient subjects among

men in each category. In fact, the question of what constitutes deficiency in women is difficult to answer since all seven normal women with α_2 -PAG concentrations below the 95% prediction limits (Fig. 2) had higher levels of the protein than occur in many men. Possibly, the deficiency in women arises at a higher concentration than in men, but as the medical history of these seven women and the four normal men with low α_2 -PAG concentration is unknown, it was impossible to ascertain whether any of them had had a history of food intolerance or gastrointestinal disorders, for example.

Interestingly, the only case of complete deficiency of α_2 -PAG was found in a severely ill woman who died of respiratory failure and who had had a history of intractable diarrhoea. Obviously we would be very interested to identify other cases of total deficiency and to compare the clinical histories of such subjects with that of this patient. It would also be important to determine whether cells producing α_2 -PAG could be detected in the gut mucosa of subjects deficient in α_2 -PAG, as serum IgA deficiency can occur without concomitant mucosal IgA deficiency.¹⁷

Overall, the incidence of α_2 -PAG deficiency in patients suffering from the conditions listed in Table 1 was two and a half times greater than that in the normal population (10.1% compared with 4.1%). If only the male patients in Table 1 are considered, however, the incidence rises to six times that of normal men (17.1% compared with 2.8%). Although the precise incidence of α_2 -PAG deficiency occurring in association with gastrointestinal disease is uncertain, the relative ease with which we were able to identify deficient subjects suggests that it must be several times greater than the incidence of selective IgA deficiency, which is reportedly present in 1 in 700 of the normal population.¹⁷ Equally, we are still uncertain as to what proportion of the subjects with α_2 -PAG deficiency had associated disease.

Clearly, there are many patients with other forms of gastrointestinal disease whom we would like screened for deficiency of this serum protein. It is evident that in this study the strongest association was between α_2 -PAG deficiency and dermatitis herpetiformis: three of 12 men (25%) were deficient and had urticaria, two of five (40%) of men were deficient; two of the original

group of patients said to have dermatitis herpetiformis were later found to have been misclassified and had a history of urticaria. It is worthwhile noting that in many cases of urticaria the antigens, which trigger this type I hypersensitivity reaction are foodstuffs such as strawberries and shellfish. This may lend support to the idea that α_2 -PAG could, indeed, play a part in protecting the gut mucosa from being overstimulated by food antigens.

In earlier studies^{9,10} we showed that there were moderate to high concentrations of α_2 -PAG in colostrum and breast milk, although our immunohistochemical studies have failed to find any evidence of cells positive for α_2 -PAG cells in the fetal gut mucosa. Possibly, therefore, the α_2 -PAG in colostrum could prevent overstimulation of the neonatal gastrointestinal tract by dietary antigens.

The precise biological role of α_2 -PAG has yet to be determined, but considering its recognised immunosuppressive properties,¹¹⁻¹³ its association with plasma cells that produce IgA in the lamina propria, and the clinical data presented here, it is not unreasonable to suppose that it has a part in the regulation of gut mucosal immunity. There are, however, many unanswered questions, certain of which are currently under investigation, including whether deficiency of α_2 -PAG precedes a disease process or is simply a secondary phenomenon.

We thank all those who helped with the collection of serum samples, including Dr Ronald Davidson and the staff of the department of haematology, Aberdeen, who collected the normal range. We thank too, Dr DR Appleton for help with the statistical work.

LMG was supported by the Scottish Hospitals Endowments Research Trust and SSA was in receipt of a studentship from the Medical Research Council.

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Requests for reprints to: Professor CHW Horne, Department of Pathology, Royal Victoria Infirmary, Newcastle upon Tyne, NE1 4LP, England.