

Plasma β_1C - β_1A globulins and immunoglobulins in coeliac disease

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Carswell, F., and Logan, R. W. (1973). *Archives of Disease in Childhood*, 48, 587. **Plasma β_1C - β_1A globulins and immunoglobulins in coeliac disease.** The plasma β_1C - β_1A globulins, IgA, IgG, and IgM concentrations were estimated in 55 untreated children with coeliac disease and in 33 other children. There was a lower level of β_1C - β_1A globulins and a higher level of IgA in the plasma of the children with coeliac disease. These findings support the theory that an immune reaction is involved in the pathogenesis of coeliac disease.

The aetiological basis of coeliac disease remains a mystery, but some authors (Beale *et al.*, 1971; Hobbs, 1971) have suggested that the disease could arise because the IgA produced by these patients fails to inactivate and detoxicate gluten.

There is evidence of abnormal IgA activity in coeliac patients. Thus, there is often a high IgA level in the plasma of patients with coeliac disease (Asquith, Thomson, and Cooke, 1969; Hobbs, 1969), and this tends to return to normal on successful treatment with a gluten-free diet (Visakorpi, Kuitunen, and Pelkonen, 1970). A small but significant proportion of patients with coeliac disease have a subnormal plasma level of IgA on diagnosis (Visakorpi *et al.*, 1970; Mawhinney and Tomkin, 1971). Patients are also said to have a subnormal IgA response to the oral administration of poliovirus (Beale *et al.*, 1971).

It is postulated (Beale *et al.*, 1971; Hobbs, 1971) that in coeliac disease the malfunctioning IgA fails to prevent the penetration of the small bowel mucosa by gluten ingested in the diet. There is said to be an increased proportion of IgM-containing plasma cells and increased IgM in the duodenal juice in adult patients with coeliac disease (Hobbs *et al.*, 1969). Jos, Rey, and Frezal (1972) and Savilahti, Kuitunen, and Visakorpi (1973) have confirmed that there is an increase in the proportion of IgM-containing cells in the mucosa, but also found an increased number of IgA-containing cells in children with coeliac disease. The increased IgM is said to take over the role of the dysfunctioning IgA in coeliac patients (Hobbs, 1971). However, it is

inefficient in detoxicating the gluten in the small bowel, and instead it binds the gluten in the lamina propria. A submucosal Arthus reaction occurs and damages the mucosa (Asquith and Cooke, 1969; Beale *et al.*, 1971; Hobbs, 1971). Complement would be fixed in this type of reaction.

Shmerling and Shiner (1970) have shown that the first changes resulting in the intestinal mucosa of coeliac children on reintroduction of gluten occurred in the basement membrane. They therefore suggested that the pathological changes were consistent with a delayed type immunological response taking place primarily in the lamina propria. As Rubin *et al.* (1965) had previously failed to find localized complement-fixing aggregations in the submucosa of patients with coeliac disease, we decided to estimate the concentration of β_1C - β_1A globulins in the plasma of patients with coeliac disease in the expectation that consumption of complement in the lamina propria would lead to a finding of a low concentration in the plasma.

Methods

Immunoglobulin and β_1C - β_1A globulin concentrations were estimated by a Mancini technique using commercial Behringwerke (Hoechst) plates and standards. Plasma specimens for analysis were stored at +4 °C for up to 24 hours. It is probable that conversion of the β_1C globulins to β_1A globulins occurred before analysis. Diffusion was allowed to proceed to completion at +4 °C before measurement. Where prolonged storage of plasma specimens was required, the samples were kept at -25 °C.

A detailed account of the standardization of the immunoglobulin determination with the normal ranges

so derived has already been published (Urquhart, Logan, and Izatt, 1971).

Upper small bowel biopsies were performed on 88 patients while on gluten-containing diets because of suspected coeliac disease. The 55 patients with an abnormally flat biopsy, a clinical response to a gluten-free diet, and supporting evidence of malabsorption were classified as suffering from coeliac disease. The diagnoses in the 33 'control' patients who had a normal or near normal small bowel biopsy are listed in Table I. Several patients had multiple diagnoses, each one of which is shown in Table I.

The age and sex distribution of the coeliac and control patients are compared in the Fig. There is no significant difference between the two groups in sex (Yates' χ^2 test) or age (Student's 't' and Wilcoxon's sum of ranks tests).

Several faecal samples and duodenal juice obtained at biopsy were cultured for pathogenic organisms and examined for *Giardia lamblia*, and biopsies were examined for giardia infestation.

Results

The plasma immunoglobulin and $\beta_1C-\beta_1A$ concentrations in the coeliac and control groups are shown in the Fig. The mean $\beta_1C-\beta_1A$ concentration is significantly lower (108 mg/100 ml vs 121 mg/100 ml) and the mean IgA level is significantly higher (131 mg/100 ml vs 98 mg/100 ml) in the coeliac group, but there are no significant differences between the mean IgG and IgM concentrations in the two populations. (Both Wilcoxon's sum of ranks test and Student's 't' test were used and a 'P' of <0.05 was taken as significant.)

TABLE I

Eventual diagnoses in 33 patients who did not have coeliac disease

Diagnosis	No. of patients
<i>A. 22 patients with probable gastrointestinal disease</i>	
<i>Giardia lamblia</i> infestation	11
Psychosocial diarrhoea*	8
Post-gastroenteritis syndrome	2
Cystic fibrosis	2
Milroy's disease with gut involvement	1
Sex-linked a- γ -globulinaemia	1
Low birthweight dwarfism	1
Constitutional dwarfism (small parents)	1
Hypothalamic astrocytoma	1
Familial hypophosphataemic rickets	1
Iron deficiency malabsorption	1
<i>B. 11 patients with no gastrointestinal disease</i>	
No abnormality detected	6
Low birthweight dwarfism	2
Constitutional dwarfism (small parents)	2
Transient gluten intolerance	1
Malnutrition	1

*This group includes children of small size with severely disrupted family life and history of diarrhoea as outpatients. They rapidly gained weight and did not have diarrhoea as inpatients, though they not infrequently also had giardiasis.

One patient in the control group had sex-linked familial a- γ -globulinaemia and a $\beta_1C-\beta_1A$ result of 162 mg/100 ml. One patient included in the coeliac group had an isolated IgA deficiency and $\beta_1C-\beta_1A$ globulins of 108 mg/100 ml. Another 33-month-old patient in the coeliac group had a severe protein-losing enteropathy and plasma

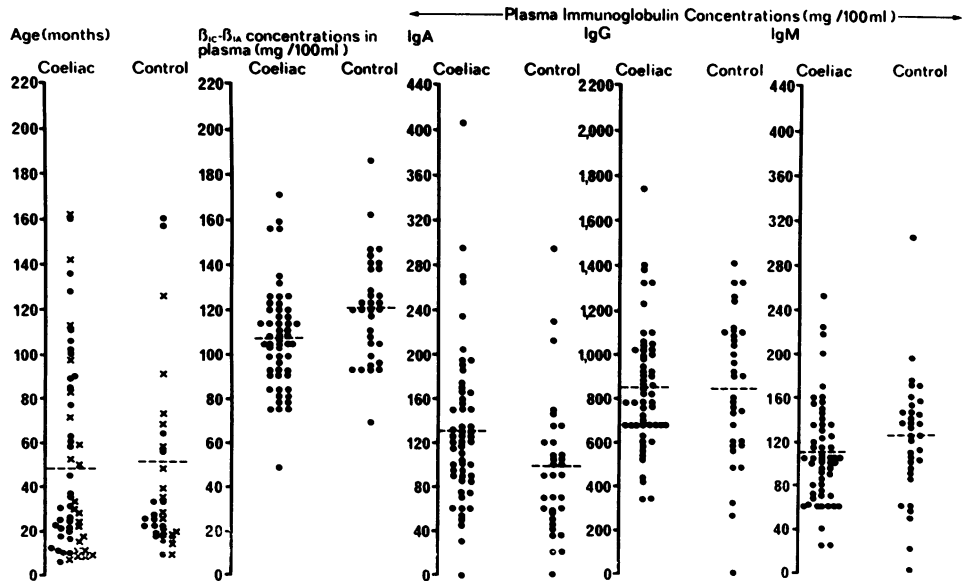


FIG.—Graph of the age (in months) and sex (● male, X female), plasma $\beta_1C-\beta_1A$ globulins (●) and immunoglobulin (●) concentrations (mg/100 ml) in coeliac and in control groups. Arithmetic mean values are indicated by broken lines.

$\beta_1C-\beta_1A$ globulins of 75 mg/100 ml. This patient's immunoglobulin concentrations were IgA 235 mg/100 ml (high), IgG 420 mg/100 ml (low normal), IgM 135 mg/100 ml (high normal). The mean $\beta_1C-\beta_1A$ globulin concentration in the patients who did not have gastrointestinal disease (Table I, B) was 121 mg/100 ml.

The infections present at the time of diagnosis are shown in Table II. One child with coeliac disease

TABLE II

Percentage incidence and fraction of patients with bowel infections in the population studied

Infecting agent	Coeliac (%)	Control (%)
<i>Giardia lamblia</i>	24 (13/55)	33 (11/33)
<i>Shigella</i> (<i>sonnei</i> and <i>flexneri</i>)	4 (2/55)	0 (0/33)
Enteropathic <i>Esch. coli</i> (055, 0112, 0127)	4 (2/55)	3 (1/33)

also had hydronephrosis and urinary tract infection with *Esch. coli* and *Proteus mirabilis*. The mean plasma $\beta_1C-\beta_1A$ globulin concentrations in the patients with infections or *Giardia lamblia* infestation, or without any evidence of infection, did not differ significantly. So, too, the values in the noncoeliac disease groups A and B (Table I) did not show significant differences.

Discussion

The level of $\beta_1C-\beta_1A$ globulins was lower in coeliac patients than in the control group as a consequence of either reduced production or increased consumption. In our series there was a lower mean IgM concentration in the coeliac patients (Fig.), though the difference was not statistically significant. The IgG plasma concentrations were virtually identical in our two groups. It is not possible in the present series to decide whether the low concentration of the plasma $\beta_1C-\beta_1A$ globulins reflects increased consumption or reduced synthesis. It is of interest that our patient with severe protein-losing enteropathy could at least increase her synthesis of IgA and IgM sufficiently to maintain high levels despite the excessive loss of globulin into the bowel (Hobbs, 1969).

The whole coeliac population has a higher mean serum IgA level than the control population. The finding of a low concentration of $\beta_1C-\beta_1A$ globulins in the plasma of patients with coeliac disease is consistent with the theory that coeliac disease is due

to an Arthus-type reaction in the lamina propria between immunoglobulins, antigens and complement. The resulting complex is thought to damage the enterocytes (Beale *et al.*, 1971; Hobbs, 1971).

Our studies do not show any significant correlation between infection and low complement levels, and it therefore seems unlikely that the lower $\beta_1C-\beta_1A$ concentrations found in the coeliac population are due to infection. The possibility exists that complement is bound to the food antibodies already described (Taylor *et al.*, 1961; Ferguson and Carswell, 1972) and may not be relevant to the primary pathogenesis of coeliac disease.

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