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Editorial

Circulating Immune Complexes in Diabetes

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Over the last few years more sensitive, reproducible and in some instances more specific techniques for the detection of circulating immune complexes (AgAb) have been developed [1–4]. Using these newer techniques immunological aspects of various diseases have been reappraised, and the presence of AgAb in diabetes has also been investigated.

The interest in immune phenomena in diabetes has been increasing progressively. In the 1960s several studies, originating from the immunological implications of heterologous insulin administration, suggested that immune mechanisms could be of importance in the aetiology of diabetic microangiopathy. Morphological similarities with other immunological disorders were described [5–7], immune components were found in microangiopathic vessels [8–11], and diabetic – like lesions were experimentally induced by immune mechanisms especially in the renal glomeruli [12–14].

In the 1970s works by different authors provided a completely new outlook on the pathogenesis of insulin dependent diabetes. Clinical studies had shown a suggestive relationship between insulin-dependent diabetes and other organ specific autoimmune diseases [15, 16]. It was then reported that in insulin-dependent diabetes [17–18] there was a modification in the cell-mediated immune response [19–21], an association with particular HLA antigens [22–24], and finally the presence of autoantibodies against islet cells was demonstrated [25–27].

In 1977 Irvine et al. using a single sensitive method [28] reported an increase in circulating immune complexes (AgAb) in some insulin-dependent diabetics at the time of diagnosis as well as in treated diabetics. Since then other investigators have confirmed an increase in AgAb in many diabetics, and have shown a correlation between the presence of AgAb and various diabetic conditions [29–39].

Before proceeding further it is necessary to delineate precisely what can be measured by the AgAb methods. The solid phase CIq binding test, the Raji cell radioimmune assay and the conglutinin binding assay are some of the most sensitive techniques presently available [4, 40]. These methods are antigen non – specific and may be influenced by immunoglobulin aggregates but not by DNA, bacterial endotoxins and heat induced aggregates. The CIq method detects mainly complexes in antigen excess through the Fc portion of immunoglobulin aggregates, whilst the other two methods reveal complexes near the equivalence point, mostly through the third component of the complement. The complexes detected by all these methods are potentially harmful since they may activate the complement system or react with those cells bearing receptors for complexed immunoglobulins or the complex bound complement (namely lymphocytes and macrophages). The antigens involved in the complex formation may be either part of a cell membrane and secondarily shed into the circulation as a complex or non-cell-bound antigens. In the latter situation complexes may be formed either in the circulation, with subsequent localisation in vessel walls or perivascular tissues, or locally in certain organs or tissues. As the methods presently available do not distinguish between complexes related to specific disease processes and those found in other more common conditions, e.g. viral infections, it is not surprising that circulating AgAb are also found in some apparently healthy subjects. Thus in evaluating the presence of AgAb in a particular disease it is important to compare the results with those found in a large normal population and to select an appropriate limit of positivity [41]. Differences in these basic points may explain some of the discrepancies between the various reported data.

In 1978 the increase in circulating AgAb in newly diagnosed insulin-dependent diabetics was confirmed in a large series of patients compared with age-matched healthy controls using two different and sensitive methods [35]. In most of the patients AgAb

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tend to disappear within a few months of diagnosis and the decline is similar to that of islet cell antibodies (ICAb). Interestingly a significant association between the presence of AgAb and the occurrence of ICAb has been found at diagnosis and over the next few months. It is of particular interest that in a minority of insulin-dependent diabetics in which ICAb persist for some years after diagnosis circulating AgAb are increased [36]. The presence of circulating AgAb in newly diagnosed and untreated insulin-dependent diabetics did not correlate with titres of antivirus antibodies or with insulin antibody levels in insulin-treated diabetics within the first year of diagnosis (unpublished observations).

The significance of the presence of soluble AgAb in the serum of a large number of insulin-dependent diabetics near the time of diagnosis could be explained simply as a secondary effect of the immunopathological phenomena occurring in the islets or as a consequence of a normal immune response towards exogenous agents or viruses. AgAb, on the other hand, could be involved in the islet cell damage through the activation of plasma components or of cells. The temporary presence of AgAb at the time of diagnosis of insulin-dependent diabetes may tie together some of the histological and immunological findings in the pathogenesis of this form of diabetes: the transient lymphocytic infiltration [42], the temporary presence of antibodies reacting with islets [27, 43, 44], and the increased K-cell activity in newly diagnosed cases [44, 45].

The presence of circulating AgAb has also been reported in a small but statistically significant percentage of diabetics [31, 33, 34] more than one year after diagnosis. Theoretically various factors might influence the formation of circulating AgAb, namely age and sex of the patient, type of treatment, insulin antibody levels, degree of metabolic control, latent infections, and the presence of complications. Studies using a Clq method on a randomly selected diabetic population have revealed an increase in circulating AgAb in insulin-treated diabetics, expecially in those with a duration of disease between 10 and 20 years compared with diabetics treated by diet or oral hypoglycaemic agents [38]. Furthermore a correlation between insulin antibody titres and AgAb levels has been reported. Complexes in diabetics with high insulin binding capacity levels tend to be undetectable by Clq methods [46]). This negative correlation may possibly be explained by the presence of low affinity insulin antibodies, the antigenic bivalency of insulin and the fact that Clq detects complexes in Ag excess. Thus data presently available suggest that at least some of the AgAb found in insulin treated diabetics are related to insulin treatment.

Circulating AgAb have also been studied in patients with late diabetic complications. In the past the presence of circulating complexes was suggested in order to explain a few clinical, morphological and experimental findings in patients with severe microangiopathy [47, 48, 49]. These studies present various difficulties because of the many factors involved in diabetic microangiopathy and the variables that should be taken into account. The type of diabetes, the different types of treatment, the time from diagnosis, the degree of metabolic control, and the type and severity of complications are of importance in these studies. The results in the literature are contradictory. Nevertheless when selected groups of diabetics with microangiopathy have been studied using a technique based on C1q properties, a correlation appears between the presence of AgAb and the occurrence of severe microangiopathy. AgAb were significantly lower in long-standing diabetics with no sign of microangiopathy than in comparable diabetics with severe microangiopathy (either proliferative retinopathy or severe nephropathy). AgAb were significantly higher in diabetics presenting with severe retinopathy within a few years of diagnosis including malignant microangiopathy [50] than in comparable diabetics without microangiopathy [37, 39]. AgAb found in patients with severe microangiopathy do not seem to have any correlation with the type of treatment or the insulin antibody titres. This finding is in keeping with the clinical observation that microangiopathy occurs irrespective of the type of treatment. These results suggest that a heterogeneous population of immune complexes, most of which are not related to insulin treatment, are present in certain patients with severe microangiopathy. Enhancement of AgAb levels could be due to an increased rate of production or a decreased rate of clearance of the complexes. As most AgAb detected by currently available methods are cleared by the reticuloendothelial cells lining the blood vessels, it is worth noting that impaired phagocytic clearance seems to be present in the majority of patients with severe microangiopathy [39].

According to the present state of our knowledge, it is tempting to speculate that an increase in soluble antigen-antibody complexes (due to impaired phagocytic clearance) in patients with severe microangiopathy may contribute to the vascular damage after passive binding or trapping of AgAb in the small vessel walls and in the perivascular tissues.

At present the detection of circulating antigen-non-specific complexes is an unsatisfactory indirect measurement of more complex immune phenomena occurring elsewhere. Purification and identification of antigens involved in the complexes, careful follow-

up of patients and a better understanding of the dynamics involved in the formation and clearance of AgAb are now necessary in order to evaluate the significance of immune complexes in diabetes.

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