Immunological Phenomena in Patients with Diabetic Nephropathy

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Abstract

Diabetic nephropathy (DN) is one of the main causes of chronic renal failure. A wide range of autoantibodies have been described in DN patients, associated with the progression and duration of diabetes, diabetic complications and with the development of additional autoimmune glomerular disease superimposed upon DN. The aim of our study was to investigate the prevalence and clinical significance of some immunological markers in DN patients. We investigated the prevalence of ANA, ANCA, anticardiolipin, anti-beta-2-glycoprotein-I, anti-ds-DNA, anti-ss-DNA, Sm, RNP, Ro, La antibodies, serum cryoglobulin levels, RF, C3 and C4 complement fractions, HBs antigen, and anti-HCV antibodies in 16 patients with biopsy-proven DN (12 female and 4 male, mean age 45.6 +/- 13.6 years). The results were compared with the histological activity and chronicity indices and with the clinical and laboratory data. We found positive ANA in 3 patients with type I diabetes and autoimmune thyroid disease (autoimmune polyglandular syndrome type IIIA). ANA correlated with the histological activity index (p<0.05) but showed no correlation with the laboratory data and histological chronicity index. All 3 patients were on oral L-thyroxin substitution. ANCA were positive in 3 other patients – 1 with type I and two with type II diabetes. ANCA showed no correlation with histological or laboratory parameters. All other autoantibodies, HBs antigen and anti-HCV antibodies were negative, RF, cryoglobulin, C3 and C4 serum levels were within the normal range in all patients. The authors discuss the significance of ANA in patients with DN and autoimmune polyglandular syndromes.

Materials and methods

We evaluated the sera of 16 diabetic patients (12 female, 4 male, 8 with IDDM and 8 with NIDDM, mean age 45.6 +/- 13.6 years, mean duration of diabetes 136.6 +/- 90.9 months, 3 patients had autoimmune polyglandular syndrome type III A) with biopsy-proven DN (mean histological activity index 5.1 +/- 1.9, mean chronicity index 4.1 +/- 2.3) for the presence of the following autoantibodies: ANA (indirect immunofluorescence on Hep-2), ANCA (indirect immunofluorescence on ethanol-fixed human neutrophils), IgG and IgM anticardiolipin (ACL) and anti-beta-2-glycoprotein-I (beta-2-GP-I) antibodies – ELISA method, ds- and ss-DNA, Sm, RNP, Ro, La – counter immunoelectrophoresis, cryoglobulins (CG, spectrophotometric analysis), RF (latex agglutination), C3 and C4 complement levels (radial immunodiffusion). All patients were tested for HBs antigen and anti-HCV IgG and IgM antibodies. The results were compared with the histological activity and chronicity indices [10] and with the clinical and laboratory data of the patients. The statistic analysis was performed with computer statistic program SPSS 11.0 for Windows.

Results

• We found positive ANA in three female patients with IDDM and autoimmune thyroid disease (autoimmune polyglandular syndrome type III A, on L-thyroxin substitution) – two with Hashimoto’s thyroiditis and one with Graves’–Basedow’s disease and thyroid-associated ophthalmpathy (TAO). One of these patients subsequently went on haemodialysis.

• Positive ANCA were found in another three patients – two with NIDDM and one with IDDM. The latter patient subsequently went on haemodialysis.

• ACL, beta-2-GP-I, RF, CG, C3 and C4 were within the normal limits in all patients;

• ds-DNA, ss-DNA, Sm, RNP, Ro, La and hepatitis markers were negative in all the investigated subjects.

Discussion

DN is among the main causes of ESRD [1, 4]. Two separate phases and 5 histological stages in the development of DN are recognized: early phase (manifested by microalbuminuria, hyperfiltration and nephromegaly, histological data for capillary basement membrane thickening and mesangial expansion) and advanced DN (proteinuria, hypertension and renal failure with histological data for diabetic glomerulosclerosis) [1]. In some patients with IDDM and NIDDM the development of superimposed immune glomerulonephritis (GN) and other non-immune nephropathies has been described, including focal and segmental glomerulosclerosis, IgA GN, acute postinfectious GN, mesangioproliferative GN, rapidly progressive GN, minimal-change nephropathy.

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lupus nephritis, Henoch-Schönlein vasculitis, chronic pyelonephritis, hypertensive and hyperuricemic nephropathy, accelerated atherosclerosis and ischaemic kidney disease, chronic tubulo-interstitial nephritis, drug-induced kidney diseases, HCV- and HBV-associated nephritis, cryoglobulinemic nephritis, etc. [1, 4, 6, 11-16].

The detection of active urinary sediment and/or the rapid deterioration of renal function especially in IDDM patients with short duration of diabetes and/or associated autoimmune disease should prompt the physician towards the search of immune-mediated glomerular disease. According to Cavallo et al. [11] the functional and biochemical changes in the diabetic kidney predispose it to a secondary immune-mediated injury. The development of immune GN is found more frequently in patients with IDDM and autoimmune polyglandular syndrome type IIIA and received L-thyroxin substitution treatment. The occurrence of these autoantibodies in the described patients could be associated with the development of a multiple autoimmune disease. In favor of this hypothesis is the presence of autoimmune thyroid disease and the association of ANA with the histological activity index. On the other hand, all ANA-positive patients received L-thyroxin, and therefore the autoantibodies could be drug-induced.

According to the literature, positive ANCA in DM patients are associated with the development of rapidly progressive and segmental necrotizing GN with or without pulmo-renal syndrome [4, 14]. None of our ANCA-positive patients had such histological changes.

**Conclusion**

The detection of positive autoantibodies in DM patients should prompt the investigator towards the search of another organ-specific (in the context of autoimmune polyglandular syndrome) or non-organ specific autoimmune disease or immune-mediated GN superimposed upon DN. The association of IDDM and autoimmune thyroid disease with positive ANA in three of our patients (1 of them with TAO) and the correlation between positive ANA and histological activity index supports the hypothesis of the polyclonal acceleration of the organ-specific autoimmune diseases that is demonstrated by the production of organ-specific and non-organ-specific autoantibodies and a gradual widening of the spectrum of autoimmune aggression [21]. On the other hand, the detection of positive ANA in patients with Graves’-Basedow’s disease, TAO and DN in IDDM supports the theory of the systemic nature of the disease caused by polyclonal ANA cross-reacting with tissue-specific membrane proteins in the thyroid gland, connective-tissue structures of the skin, the orbit and other tissues [22].

**References**


