Original Article

Prospective study on renal outcome of IgA nephropathy superimposed on diabetic glomerulosclerosis in type 2 diabetic patients

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Abstract

Background and methods. In order to examine the clinical outcome of IgA nephropathy (IgAN) superimposed on diabetic glomerulosclerosis in type 2 patients we studied 36 Chinese patients (26 men, 10 women), who were recruited for renal biopsy when they had proteinuria of more than 1 g/day. Twenty-seven had isolated diabetic glomerulosclerosis and nine had IgAN superimposed on diabetic glomerulosclerosis (combined). Renal function was assessed by serum creatinine, 24-h urine protein and creatinine measurements. Patient survival rate, incidence of end-stage renal disease (ESRD), blood pressure, and glycaemic control status were determined.

Results. The age at the time of renal biopsy was younger for the combined group when compared with the diabetic glomerulosclerosis group (44 ± 3.6 vs 58 ± 2.1 years, \( P = 0.006 \)). The duration of diabetes was, however, similar for the two groups (8.0 ± 2.3 vs 6.7 ± 1.2 years, \( P = \text{NS} \)). After a mean follow-up of 31.6 ± 15.3 months, 15 patients (one in the combined group and 14 in the diabetic glomerulosclerosis group) developed ESRD. Nine patients (all in the diabetic glomerulosclerosis group) died during follow-up. With similar glycaemic and blood pressure control, the two groups had comparable rate of decline of creatinine clearance (CrCl) \((-0.73 ± 0.26 \text{ vs } -0.73 ± 0.18 \text{ ml/min/1.73 m}^2/\text{month}, \ P = \text{NS})\), final serum creatinine \((363 ± 134 \text{ vs } 426 ± 52 \mu\text{mol/l}, \ P = \text{NS})\) and proteinuria levels \((4.3 ± 0.9 \text{ vs } 4.4 ± 0.6 \text{ g/day}, \ P = \text{NS})\), as well as CrCl \((44.1 ± 19.0 \text{ vs } 33.4 ± 6.9 \text{ ml/min/1.73 m}^2, \ P = \text{NS})\).

Conclusion. It is concluded that the superimposed IgAN does not significantly alter the medium-term clinical outcome of patients with diabetic glomerulosclerosis.

Keywords: outcome; superimposed IgA nephropathy; type 2 diabetes

Introduction

It has been shown that renal involvement in type 2 (non-insulin-dependent) diabetes mellitus patients does not necessarily indicate diabetic nephropathy. We have found, in a prospective study of type 2 diabetic patients with proteinuria of more than 1 g/day, a 33.3% incidence of non-diabetic renal diseases [1]. IgA nephropathy (IgAN) accounted for 59% of the non-diabetic renal lesions identified. The clinical course of the combination of non-diabetic renal diseases on top of diabetic nephropathy has been described largely from retrospective series including various glomerulonephritides [2–4]. The overall result, in terms of deterioration of renal function, was therefore variable. We believe that the effects of superimposed glomerulonephritis on the progression of diabetic nephropathy depends heavily on the nature of that renal lesion, and on the time of its occurrence in the natural history of diabetic glomerulosclerosis. Isolated case reports have documented a rapid deterioration of renal function in patients with superimposed IgAN on top of diabetic nephropathy [5,6]. Lai et al. [7] have compared the 1-year outcome of seven patients with IgAN superimposed on diabetic glomerulosclerosis to patients with diabetic glomerulosclerosis alone, and found no significant differences in both final serum creatinine and creatinine clearance (CrCl). The existing data is scarce considering IgAN is the most common glomerulonephritis in the world [8]. From the patients of our prospective study, we have identified nine type 2 diabetes patients with superimposed IgAN. We have performed a prospective observational study on the clinical outcome of this group of patients compared with 27 patients with isolated diabetic glomerulosclerosis.

Subjects and methods

Patients

All 51 patients who entered the study on incidence of non-diabetic renal disease in type 2 diabetes [1] were considered for this observational extension of study, in which renal
function was assessed by serial serum creatinine concentrations and 24-h urine protein and creatinine measurements. Patient survival rate, incidence of end-stage renal disease (ESRD), blood pressure, and diabetic control status were determined. Seven of the original 34 patients with diabetic glomerulosclerosis (diabetic glomerulosclerosis group) were lost to follow-up within 18 months after renal biopsy and were excluded from the analysis. Nine patients with combined IgAN and diabetic glomerulosclerosis (combined group) were identified. Briefly, they are all Chinese diabetic patients with renal involvement referred to our renal unit during the period from April 1995 to January 1997. They were enrolled when they had proteinuria of > 1 g/day. Renal biopsies were examined by light microscopy (haematoxylin-eosin, periodic acid-methenamine silver, periodic acid-Schiff and the Congo red staining), immunofluorescent microscopy or immunoperoxidase staining (monospecific rabbit anti-human IgG, IgA, IgM, C1q, C3, and fibrinogen antisera) and electron microscopy (material fixed in 2.5% glutaraldehyde and embedded in resin). All biopsies were found suitable for a definitive diagnosis and reviewed by two independent pathologists. Diabetic nephropathy was diagnosed by the presence of mesangial expansion and diffuse intercapillary glomerulosclerosis, with or without the nodular Kimmelstiel–Wilson formation, basement membrane thickening, fibrin caps, or capsular drops. IgAN was diagnosed when solely or predominantly IgA-containing immune complexes were detected in the mesangium by both immunofluorescent and electron microscopies [9]. All patients had adult-onset type 2 diabetes with no history of alcoholism, liver disease, dermatitis herpetiformis, or coeliac disease.

The following data were recorded at the time of renal biopsy: age, age at onset of diabetes, duration of diabetes, serum urea, creatinine and albumin levels, fasting venous plasma glucose, glycylsylated haemoglobin (HbA1c, normal range 4.1–6.1%), serum IgA level (normal range 0.89–4.46 g/l), urine microscopy, 24-h proteinuria, CrCl. Onset of DM was the time when DM was first diagnosed. DM duration was the period between the age of onset and renal biopsy. Haematuria was defined by more than 10 red cells per micro-litre on phase contrast urine microscopy. Hypertension was diagnosed when sequential diastolic blood pressure readings were 90 mmHg or higher, or when systolic blood pressure readings were greater than 140 mmHg [10].

**Study protocol**

The patients visited the renal outpatient clinic every 2–3 months. The fasting venous plasma glucose concentration, albuminuria, and arterial blood pressure were measured and the anti-diabetic and anti-hypertensive therapy adjusted. CrCl was calculated from 24-h urine creatinine excretion and the serum creatinine concentration, normalized to 1.73 m² surface area. HbA1c (normal range 4.1–6.1%) was determined every 4–6 months. Angiotensin converting enzyme (ACE) inhibitor was used in the majority of both normotensive and hypertensive patients, unless disturbing side effects or intolerance (e.g. deteriorated renal function, hyperkalaemia) occurred.

The patients’ diabetic diet was unaltered during the study, except for patients who had protein restriction when the CrCl fell below 30 ml/min/1.73 m². Patients were diagnosed as having ESRD if they became dialysis dependent, or if they died due to other causes but had renal failure (serum creatinine ≥440 mmol/l or CrCl ≤10 ml/min/1.73 m²) documented at least 1 month prior to death.

An index of the frequency of hyperglycaemia was used based on the method described [11]. Briefly, the index is the proportion of clinic visits in which severe hyperglycaemia was present. Hyperglycaemia was considered severe if the patient had a fasting venous plasma glucose value ≥10 mmol/l. The index of hyperglycaemia was the number of clinic visits with severe hyperglycaemia divided by the clinic visits with blood glucose checked during the whole follow-up period since renal biopsy.

**Statistical analysis**

The values of parameters are given as mean (± standard error of mean (SEM)) where appropriate. Differences between groups were assessed by non-parametric statistical tests: Fisher’s exact test, χ² test or Mann–Whitney U test where appropriate. Linear regression analysis was used to estimate the rate of change in CrCl for each patient using all measurements of glomerular filtration rate. Comparisons of the end points of ESRD or death between the two groups were made using the log-rank test, wherein patients were censored at last follow-up. Using the Cox regression model, survival rates were adjusted for the covariables: age, systolic and diastolic blood pressures, baseline CrCl at time of renal biopsy, averaged fasting blood glucose level and the two groups (combined or diabetic glomerulosclerosis). Statistical significance was assumed at a P value <0.05 (two-tailed).

**Results**

**Patient profile at renal biopsy**

The diabetic patients studied are all Chinese (26 men and 10 women). Twenty-seven patients had isolated diabetic glomerulosclerosis and nine combined IgAN and diabetic glomerulosclerosis (Table 1). The age at the time of renal biopsy was younger for the combined group when compared with the diabetic glomerulosclerosis group (44 ± 3.6 vs 58 ± 2.1 years, P = 0.006). The duration of DM was, however, similar for the two groups (8.0 ± 2.3 vs 6.7 ± 1.2 years, P = NS). The combined group had a higher incidence of microscopic haematuria and a lower level of baseline proteinuria than the diabetic glomerulosclerosis group (67 vs 26%, P = 0.046; 2.7 ± 0.7 vs 6.2 ± 0.8 g/day, P = 0.015). The baseline serum creatinine, IgA level, and CrCl were similar for the two groups (138 ± 32 vs 164 ± 15 mmol/l, P = NS; 3.73 ± 0.60 vs 3.42 ± 0.26 g/l, P = NS; 73.1 ± 11.1 vs 60.2 ± 7.0 ml/min/1.73 m², P = NS, respectively).

**Follow-up of patients**

All patients were followed-up in the same renal unit, for an average of 31.6 months (range 6.2–54.7). The duration of follow-up was similar for the two groups (34.1 ± 6.2 vs 30.8 ± 2.9 months, P = NS). There was no difference between combined and diabetic glomerulosclerosis patients with regards to the mean systolic and diastolic blood pressures, number of hypertensive drugs used as well as the percentage of patients on ACE inhibitors (Table 2). The two groups had comparable
level of glucose control as measured by averaged fasting blood glucose level and averaged HbA1c (10.1 ± 1.1 vs 8.2 ± 0.4 mmol/l, *P* = NS; 9.87 ± 0.67 vs 8.64 ± 0.37%, *P* = NS, respectively). No significant difference was present in the index of hyperglycaemia between the two groups. None of the combined group patients had received treatment specific for IgAN, as decided by the attending physicians.

### Outcome of diabetic glomerulocerosclerosis patients with and without IgAN

Fifteen patients (14 in the diabetic glomerulosclerosis group and one in the combined group) developed ESRD during follow-up (log-rank survival analysis, *P* = 0.0393) (Figure 1). Nine patients (all in the diabetic glomerulosclerosis group) died during follow-up (log-rank survival analysis, *P* = 0.0615) (Figure 2). Eight of them refused renal replacement therapy because of co-morbidities and one had refractory congestive heart failure.

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**Table 1.** Baseline patient demographics at time of renal biopsy

|                          | IgAN + diabetic glomerulosclerosis (*n* = 9) | Isolated diabetic glomerulosclerosis (*n* = 27) | *P*  
|--------------------------|---------------------------------------------|----------------------------------------------|------
| Sex (M:F)                | 7:2                                         | 19:8                                         | NS   
| Age (year)               | 44 ± 3.6                                    | 58 ± 2.1                                    | 0.006
| DM duration (year)       | 8.0 ± 2.3                                   | 6.7 ± 1.2                                   | NS   
| Microscopic haematuria   | 6 (67%)                                     | 7 (26%)                                     | 0.046
| Baseline serum creatinine (µmol/l) | 138 ± 32                               | 164 ± 15                                    | NS   
| Baseline proteinuria (g/day) | 2.7 ± 0.7                               | 6.2 ± 0.8                                   | 0.015
| IgA level (g/l)          | 3.73 ± 0.60                                 | 3.42 ± 0.26                                 | NS   
| Baseline CrCl (mL/min/1.73 m²) | 73.1 ± 11.1                           | 60.2 ± 7.0                                  | NS   

*P* value from Mann-Whitney *U* and Fisher’s exact tests; CrCl, creatinine clearance.

**Table 2.** Biochemical and outcome parameters of patients on follow-up

|                          | IgAN + diabetic glomerulosclerosis (*n* = 9) | Isolated diabetic glomerulosclerosis (*n* = 27) | *P*  
|--------------------------|---------------------------------------------|----------------------------------------------|------
| Follow-up duration (months) | 34.1 ± 6.2                                    | 30.8 ± 2.9                                   | NS   
| Mean systolic BP (mmHg)   | 150 ± 5.9                                    | 152 ± 2.8                                   | NS   
| Mean diastolic BP (mmHg)  | 78 ± 2.3                                    | 76 ± 1.7                                    | NS   
| Number of HT drugs        | 2.1 ± 0.4                                    | 1.8 ± 0.2                                   | NS   
| Usage of ACEI (%)         | 6 (67%)                                      | 18 (67%)                                    | NS   
| Mean HbA1c (%)            | 9.87 ± 0.67                                  | 8.64 ± 0.37                                 | NS   
| Mean fasting blood glucose (mmol/l) | 10.1 ± 1.1                           | 8.2 ± 0.4                                   | NS   
| Index of hyperglycaemia (%)| 19 ± 10                                      | 14 ± 9                                      | NS   
| Rate of decline of CrCl (mL/min/1.73 m²/months) | −0.73 ± 0.26                          | −0.73 ± 0.18                                | NS   
| Final serum creatinine (µmol/l) | 363 ± 134                                 | 426 ± 52                                    | NS   
| Final proteinuria (g/day) | 4.3 ± 0.9                                    | 4.4 ± 0.6                                   | NS   
| Final CrCl (mL/min/1.73 m²) | 44.1 ± 19.0                                 | 33.4 ± 6.9                                  | 0.0393
| ESRD*                    | 1                                           | 14                                          | 0.0615
| Mortality                | 0                                           | 9                                           |      

*P* value from Mann-Whitney *U* and Fisher’s exact tests.

*P* value from log-rank test.

*Defined as becoming dialysis dependent, or if they died due to other causes but had renal failure (serum creatinine ≥440 µmol/l or CrCl ≤10 mL/min/1.73 m²) documented at least 1 month prior to death.

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![Fig. 1. Proportion of patients who did not develop ESRD to last follow-up. *P* value from log-rank survival analysis.](image-url)
failure as the cause of death. Cox regression revealed that age, systolic blood pressure, and baseline CrCl (P = 0.0104, P = 0.0249 and P = 0.0012, respectively) were independent predictors of kidney survival, while systolic and diastolic blood pressures as well as baseline CrCl predicted patient survival (P = 0.0299, P = 0.0276 and P = 0.0108, respectively) (Table 3). The two groups had a similar rate of decline of CrCl (−0.73 ± 0.26 vs −0.73 ± 0.18 ml/min/1.73 m²/month, P = NS) (Figure 3). The final serum creatinine level, proteinuria level as well as CrCl at the last follow-up were also comparable for both groups (363 ± 134 vs 426 ± 52 mmol/l, P = NS; 4.3 ± 0.9 vs 4.4 ± 0.6 g/day, P = NS; 44.1 ± 19.0 vs 33.4 ± 6.9 ml/min/1.73 m², P = NS, respectively).

**Discussion**

It has been found that for type 2 diabetic patients with persistent proteinuria, the cumulative incidence of renal failure (i.e. persistent elevation of serum creatinine above 160 mmol/l) was 10.7% at 10 years and 16.8% at 15 years [12]. The average interval between onset of proteinuria to the development of renal failure was 7 years in that study. Nelson *et al.* [13] noted in Pima Indians a cumulative incidence of ESRD of 40% after 10 years and 61% after 15 years following onset of proteinuria. Using the single-shot radiochelate clearance, Gall *et al.* [14] found an average rate of decrease of glomerular filtration rate (GFR) of 5.7 ml/min/year in albuminuric type 2 diabetic patients with biopsy-proven diabetic glomerulosclerosis. The rate of loss of CrCl has been correlated to systolic and diastolic blood pressures, glycaemic control, smoking, albuminuria, and initial GFR [14–16].

Prospective studies of type 2 diabetic patients have found that 23–39% of patients with renal involvement had non-diabetic renal diseases [1,17–19]. Gall *et al.* has shown that the prognosis of the type 2 diabetic patients with non-diabetic primary renal diseases. Chiara *et al.* concluded that superimposed glomerulonephritis produced little effect on the long-term prognosis of diabetic patients except for membranoproliferative glomerulonephritis [2]. These studies included patients with different glomerular diseases and we believe that the outcome of superimposed glomerulonephritis on diabetic nephropathy should be individualized according to each type of glomerular pathology. IgAN accounts for 30% of renal biopsies in all primary glomerulonephritides both in Asia and in the world [8]. Interestingly, the coexistence of IgAN and diabetic glomerulosclerosis has only been rarely reported [1,5–7,21]. Lai *et al.* [7] followed the outcome of seven patients with combined diabetic glomerulosclerosis and IgAN for 13 months and found no effect of the superimposed IgAN on the course of diabetic glomerulosclerosis. Kawasaki *et al.* [5] reported a case of superimposed IgAN with worsened renal dysfunction in a patient with overt diabetic glomerulosclerosis. Gans *et al.* [21] suggested that the superimposed IgAN might have contributed to a decrease in renal function in two of the four patients with combined IgAN and diabetic glomerulosclerosis. Since the inclusion criteria for renal biopsy in these retrospective series have
included atypical clinical course like rapid loss of renal function among diabetic patients with renal involvement, selection bias leading to IgAN patients with aggressive renal outcome being picked up is a distinct possibility. It is apparent that only by prospectively recruiting type 2 diabetic patients with defined criteria for renal biopsy, while subsequently observing the clinical course of these patients could one determine the true difference between the outcome of patients with diabetic glomerulosclerosis alone and those with superimposed IgAN. As we have documented an apparently over representation of IgAN among Chinese type 2 diabetic population with non-diabetic renal diseases (59%) [1], such information would be of particular relevance in our context.

We have identified nine patients with combined IgAN and diabetic glomerulosclerosis and 27 with diabetic glomerulosclerosis alone from the previous study patients [1]. Seven other patients with diabetic glomerulosclerosis had not completed an 18-month follow-up after renal biopsy, and were excluded from the present study. This is to ensure enough data points for accurate estimation of rate of decline of CrCl. Three of them were transferred to other centres for follow-up for geographical reasons and the other four were lost to follow-up. There were seven patients who died and one required dialysis within 18 months of renal biopsy. They were included in the analysis in the same principle as of ‘intention-to-treat’ analysis.

Though the mean age of patients of the combined group was younger than that of diabetic glomerulosclerosis patients at the time of renal biopsy, the duration of DM before biopsy was similar. The combined group patients had a higher incidence of microscopic haematuria and a lower baseline level of proteinuria when compared with diabetic glomerulosclerosis patients, findings similar to that reported for the whole group [1].

Both groups were followed-up for a relatively long period, considering the natural history of diabetic nephropathy with macroalbuminuria. The levels of blood pressure and glycaemic control, as well as the percentage of patients on ACE inhibitors were comparable for both groups. The rate of decline of CrCl was similar for the two groups. This annual loss of 8.7 ml/min/1.73 m² is slightly higher than that reported from Caucasian series [14,16]. The baseline characteristics, as well as levels of blood pressure and glycaemic control in the present study are comparable to that in both Gall’s series and Hasslacher’s series. It is also noted that the mean weight (57 kg) and body mass index (22.5 kg/m²) of our patients are lower than that reported in Caucasian series [14,16], and thus would not explain the relatively higher rate of decline of CrCl.

Whether this is a result of racial difference is unknown. Chan et al. [22] found that Hong Kong Chinese type 2 diabetic patients had a higher prevalence of proteinuria, which in turn predicted progression to ESRD. There was no significant difference in the final serum creatinine and proteinuria of the two groups. Survival rate analysis revealed that age, systolic blood pressure, and baseline CrCl were independent predictors of kidney survival, while systolic and diastolic blood pressures as well as baseline CrCl predicted patient survival. Although the group factor was found to be a statistically significant factor for kidney survival in the model, the event rate was so low that we could not conclude on its significance. The same argument also holds for the log-rank survival analysis.

While it has been suggested that the biochemical milieu of diabetes rather than the presence of other glomerular pathology determined the overall renal outcome, one might argue that the present study has selected a relatively full-blown stage of diabetic nephropathy. We have adopted in this study the same criteria for selecting patients for renal biopsy as for any non-diabetic patient presenting with proteinuria. Yet, the mean level of proteinuria of the whole group of 36 patients was 5.32 ± 4.16 g/day at baseline. Obviously any selective referral from the diabetic clinic could not be excluded, and we believe a much more aggressive approach in terms of renal biopsy than that of the present study has to be adopted to identify the early phase of diabetic nephropathy.

IgAN is the most common primary glomerulonephritis in Hong Kong, accounting for 29.7% of all adult glomerulonephritis [23]. Even so, we have witnessed a higher than usual proportion of IgAN among our type 2 diabetic population with non-diabetic renal disease (59%) [1]. We believe that this seemingly over representation might suggest an aetiological link between the two entities. It is tempting to speculate an increased immune complex deposition in the presence of hyperfiltration, intraglomerular hypertension, as well as alteration of charge by glycated proteins in diabetes [1]. Both Ohmuro et al. and we have demonstrated that patients with diabetic nephropathy had an abnormally increased serum IgA level than matched controls [1,24]. Gans et al. [21] also suggested the coexistence of IgAN and diabetes mellitus was not mere coincidence. Functional and biochemical alterations in glomeruli of diabetic patients might facilitate the localization of immunoreactants [25,26]. Our results indicated that the medium-term renal and patient outcome of type 2 diabetic patients with combined IgAN and diabetic glomerulosclerosis were similar to that of patients with diabetic glomerulosclerosis alone. This is a study of patients with persistent proteinuria. Whether the results would be different if we were to study the early phase of diabetic nephropathy with microalbuminuria is unknown and requires further evaluation.

References


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