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Editorial Comments

The role of genetic susceptibility in diabetic nephropathy: evidence from family studies

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Introduction

Diabetic nephropathy is one of the long-term complications of both type 1 and type 2 diabetes. It is a leading cause of end-renal disease in many countries [1]. Furthermore, it is associated with increased cardiovascular mortality, with most of the excess mortality associated with diabetes being seen in those with nephropathy [2,3].

It is impossible to predict which diabetic patients will develop renal disease. Although duration of diabetes, tightness of glycaemic control, and blood pressure are undoubtedly implicated [4,5], these factors are insufficient on their own to predict which patients will develop the complication. Therefore, a patient with poor blood pressure and glycaemic control might not develop diabetic renal disease even many years after diagnosis of diabetes. Clearly, other factors must also be involved.

The prevalence of nephropathy associated with type 1 diabetes rises with increased duration but levels out at around 15 years, when a cumulative prevalence of around 50% is reached [6]; this is less easily demonstrable with regard to type 2 diabetes, where the time of onset of the disease is less clearly defined. It would appear that only a subset of diabetic patients are at risk of developing renal disease. This is in contrast to retinopathy, whose prevalence continues to rise with increased duration of diabetes so that most patients will develop the complication if they live long enough [6]. A genetic predisposition is the probable explanation. This article reviews the role of genetic susceptibility in diabetic nephropathy, concentrating on the accumulated data on inherited factors from family studies rather than on the molecular genetic studies, which have been extensively reviewed elsewhere.

Familial aggregation of diabetic nephropathy

There is a large body of evidence of familial aggregation of renal disease in type 1 diabetes (e.g. [7,8]). Data from the Diabetes Control and Complications Trial (DCCT) has also confirmed familial aggregation [9].

There is now also a growing body of evidence implicating familial aggregation of diabetic nephropathy in type 2 diabetes. Pettitt *et al.* [10] have demonstrated that in Pima Indians, proteinuria occurred in 14.3% of diabetic offspring of diabetic parents if neither parent had proteinuria, compared to 22.9 and 45.9% if one or both parents respectively had proteinuria. Such a longitudinal study would be difficult to replicate in other populations, where the onset of diabetes is at a much later age than in the Pima Indians. However, we have demonstrated that in Malta there is a higher prevalence of proteinuria in diabetic siblings of patients with diabetic nephropathy than in matched controls [11]. There is now also evidence of familial aggregation of type 2 diabetes-related renal disease in Italian, Brazilian, and Indian populations [12–14].

Co-aggregation with other manifestations of the insulin-resistance syndrome (IRS)

The inherited factors that lead to the genetic susceptibility to diabetic renal disease are uncertain. A clear candidate is hypertension, which is known to be inherited. Parental hypertension increases the risk of proteinuria in both type 1 [15,16] and type 2 [17] diabetes. These associations could be mediated by a genetic predisposition in the probands to have a higher blood pressure (even if initially it might remain within the normal range), which would contribute to the initiation and progression of renal disease. Alternatively, there could be common genetic factors that independently predispose to both hypertension and nephropathy, perhaps as part of the IRS. The finding of the EURODIAB study that the association of albuminuria with parental hypertension was not independent of hypertension in the offspring [16] suggests that the former mechanism may be more important.

Other features of the IRS also cluster with diabetic nephropathy. Diabetic nephropathy has been reported to be associated with an increased risk of cardiovascular disease in relatives in both type 1 [15] and type

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2 [17] diabetes. Parents of type 1 diabetic patients with nephropathy have also been shown to have increased mortality when compared to parents of normoalbuminuric diabetic patients [18]. Offspring of patients with diabetic nephropathy have an increased risk of diabetes [19] and there is an increased prevalence of microalbuminuria in non-diabetic offspring of diabetic patients with nephropathy [20]. Two small studies have failed to confirm that endothelial dysfunction [21] or insulin resistance [22] occur more frequently in the offspring of diabetic patients with nephropathy than in the offspring of diabetic patients without nephropathy.

Diabetic nephropathy and anthropometric parameters

One of the areas of the greatest advance recently has been work linking birth-weight and birth anthropometry to adult traits and disease. This work offers possible new insights into the predisposition to diabetic nephropathy. There is now a large body of evidence linking low birth-weight and a low ponderal index (thinness at birth) to manifestations of the IRS. These birth characteristics have been linked to increased blood pressure, abnormal glucose tolerance, cardiovascular disease, and hyperinsulinaemia [23–26]. The association of low birth-weight and/or a low ponderal index to the IRS has now been demonstrated in many populations.

The above observations have led to the 'thrifty phenotype' hypothesis. According to this hypothesis, intra-uterine malnutrition programmes the fetus to become insulin resistant. Such programming to a thrifty phenotype can be seen as adaptive as it enhances survival in circumstances of malnutrition. However, it becomes maladaptive if the individual is exposed to unrestricted food in his postnatal life.

Diabetic nephropathy has been associated with insulin resistance [27]. In view of the association of insulin resistance with both low birth-weight and with diabetic nephropathy, it was interesting to see whether birth characteristics are also associated with diabetic nephropathy. Rossing *et al.* [28] have demonstrated that such an association exists. Furthermore, short stature has been reported to be associated with an increased risk of nephropathy in both type 1 [29] and type 2 diabetes [30] as well as with microalbuminuria in non-diabetic patients [31]. As birth-weight and adult height are strongly correlated [32], height could be acting as a surrogate marker of birth-weight. It would therefore be plausible to postulate that the associations of fetal and adult anthropometry with diabetic nephropathy can be explained by a predisposition to insulin resistance. Intra-uterine growth retardation may also predispose to renal disease by resulting in a permanent nephron deficit [33].

However, some observations are not easily explained by the fetal malnutrition hypothesis. Twins have much lower birth-weights and experience greater degrees of intra-uterine malnutrition than most of those born of singleton pregnancies but Christensen *et al.* [34] have failed to detect any difference between mortality in twins and that in the general population (except for females aged 60–89 years). In addition, Williams and Poulton [35] have found that twins have a lower blood pressure at 9 and 18 years of age when compared to singletons. Subjects who were exposed to malnutrition *in utero* during the siege of Leningrad do not have higher albumin excretion rates [36].

There are other possible explanations of the observed associations between birth characteristics and features of the IRS apart from fetal malnutrition. Genetic factors also have a role in determining birth characteristics: fetal birth-weight has been shown to be positively correlated with maternal birth-weight [37] as well as with maternal height and weight at the beginning of pregnancy [38]; and both paternal birth-weight and paternal height are correlated with fetal birth-weight [39]. Maternal blood pressure during pregnancy is negatively correlated with the birth-weight of the child and positively correlated with blood pressure in the children [40], suggesting an alternative explanation of the association between low birth-weight and blood pressure to the fetal malnutrition hypothesis. Placental ratio (placental weight/birth-weight) is positively correlated with maternal body mass index but independent of parameters of maternal nutrition such as haemoglobin concentration or mean cell volume [41]. It is therefore possible that common genetic factors predispose to both low birth-weight and low ponderal index as well as features of the IRS, including diabetic nephropathy. An alternative genetic explanation to the 'fetal malnutrition hypothesis' is 'the fetal insulin hypothesis' [42] which proposes that a genetic predisposition to insulin resistance in the fetus results in reduced insulin-mediated growth *in utero* and hence lower birth-weight, as well as predisposing to insulin resistance after birth. It is likely that both the intra-uterine environment and genetic predisposition play an important role.

Is diabetic nephropathy inherited separately from diabetes?

A number of observations suggest that genes that predispose to diabetic nephropathy also predispose to type 2 diabetes. McCance *et al.* [19] have found that subjects had a greater risk of diabetes if their type 2 diabetic parents had established nephropathy, compared to those whose parents had diabetes without nephropathy. A parental history of type 2 diabetes is associated with increased risk of proteinuria in type 1 diabetic patients [43]. On the other hand, non-diabetic offspring of diabetic patients with nephropathy have a higher albumin excretion rate compared to non-diabetic offspring of diabetic patients without

nephropathy [21]. Furthermore, Freedman *et al.* [44] have reported that African Americans with end-stage renal disease (ESRD) secondary to type 2 diabetes have a relative with ESRD more commonly than do type 2 diabetic patients without nephropathy. Non-diabetic renal disease also exhibits familial aggregation [45].

One way to reconcile these observations is to hypothesize that a number of genes predispose to diabetic nephropathy and to renal disease. Some, but not all, of these genes might predispose to both the renal disease and to diabetes and other manifestations of the IRS.

Conclusion

Evidence of familial aggregation alone is not sufficient to prove genetic influences, as family members share many environmental factors as well as genetic ones. However, the consistency of the findings of familial aggregation of diabetic nephropathy and of its co-aggregation with other features of the IRS, particularly hypertension, makes a genetic component likely. The ultimate proof lies in identifying the genes responsible. This can be done either by positional cloning based on linkage analysis or by the candidate gene approach. The majority of studies to date have studied candidate genes and there are no genes where there is definitive evidence of a role in the susceptibility to diabetic nephropathy.

It is probable that a number of genes as well as environmental factors predispose to diabetic renal disease (multifactorial inheritance). From the aggregation studies outlined above, we can deduce that genes that predispose to high blood pressure, type 2 diabetes, and other manifestations of the IRS might be involved. Given our understanding of the pathogenesis of diabetic nephropathy, other candidate genes could include ones that effect intra-glomerular pressure (independently of arterial blood pressure), glomerular permeability, basement membrane thickening, and matrix expansion.

The contribution of a single gene to the development of diabetic nephropathy might be small, but diabetic nephropathy would develop in those with a combination of a number of 'bad genes' and of environmental factors (dosage effect). Environmental factors include glycaemic control, blood pressure control, and possibly intra-uterine malnutrition. If the contribution of a single gene were small, it would need large studies to be detected and replicated. The role of a number of candidate genes has mostly been explored in small case-control studies, which also have the added disadvantage of survival bias. This might explain why little progress has been made in the identifying genes responsible for diabetic nephropathy. We feel that large prospective studies, possibly investigating a number of genes, are required.

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