*Letters to the editor***Hypomagnesaemia in IDDM patients with microalbuminuria and clinical proteinuria**

Dear Sir,

Further to your recent correspondence about the frequency of hypomagnesaemia in diabetic patients and its clinical significance [1, 2], we have recently measured total serum magnesium concentrations in IDDM patients with microalbuminuria and clinical proteinuria. The latter group have a markedly increased frequency of cardiovascular disease and mortality, and are hypertensive and insulin resistant compared to IDDM patients without proteinuria.

These are features which may be associated with hypomagnesaemia [3]. Moreover, since microalbuminuria predicts the development of clinical proteinuria, it is also possible that hypomagnesaemia is more prevalent in these patients than in those without proteinuria.

We studied 16 IDDM patients with normal albumin excretion ($< 20 \mu\text{g}/\text{min}$), 16 patients with microalbuminuria ($> 20 < 200 \mu\text{g}/\text{min}$) and 16 with clinical proteinuria ($> 200 \mu\text{g}/\text{min}$). Patients were matched for age, duration of diabetes and glycated haemoglobin percentage (Table 1). Forty non-diabetic subjects of similar age were used as the reference group.

The mean serum magnesium concentration was significantly lower in each of the diabetic groups with differing renal function, than in the normal subjects. However, there was no significant difference in the serum magnesium levels amongst the diabetic groups (Table 1). None of the patients in any of the diabetic groups had a serum magnesium level lower than the mean minus 2SD for the non-diabetic subjects (0.61 mmol/l).

Although it is possible that measurements of serum ionised or intracellular free magnesium concentrations [4], rather than total serum magnesium, may reveal a more subtle difference between the patients with normoalbuminuria, microalbuminuria

and clinical proteinuria, the present data suggest that gross hypomagnesaemia is not a feature of microalbuminuria or clinical proteinuria and the decrease in the mean levels is probably not an important risk factor for the development of cardiovascular disease in these patients.

Yours sincerely,

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Selection of control subjects in genetic studies of diabetes mellitus

Dear Sir,

Pozzilli and colleagues [1] draw our attention once again to the problems of assembling groups for the study of genetic associations in Type 1 (insulin-dependent) diabetes. The importance of ethnic matching is irrefutable but we would suggest that difficulties are not limited to the control group – significant problems may arise in the collection of affected subjects.

There is considerable evidence that both Type 1 and Type 2 (non-insulin-dependent) diabetes are heterogenous categories

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Table 1. Clinical features and serum magnesium concentrations in IDDM patients subjects with normo- or microalbuminuria and clinical proteinuria, compared to normal subjects

	Age (years)	Sex (M/F)	Diabetes duration (years)	GHb (%)	Serum Mg^{2+} (mmol/l)
Non-diabetic patients ($n = 40$)	41.9 ± 10.4	19/21	–	–	1.01 ± 0.20
Normoalbuminuria ($n = 16$)	38.0 ± 9.0	11/5	20.5 ± 5.0	9.3 ± 1.3	0.79 ± 0.08^a
Microalbuminuria ($n = 16$)	38.7 ± 8.0	14/2	23.9 ± 7.0	9.4 ± 1.0	0.82 ± 0.09^a
Clinical proteinuria ($n = 16$)	37.9 ± 8.4	7/11	24.4 ± 5.9	9.3 ± 1.6	0.83 ± 0.11^a

^a $p < 0.001$ vs non-diabetic subjects. GHb, glycated haemoglobin. Results are mean $\pm$ SD

of disease. For example, the Type 2 diabetes phenotype may result from a variety of pathophysiological defects. There are over 70 distinct genetic syndromes associated with impaired glucose tolerance or diabetes. In some cases, different gene defects present a similar diabetic phenotype. Subjects who presented with gestational diabetes have been shown to have glucokinase and mitochondrial DNA mutations [2, 3]. Similarly, in Type 1 diabetes, insulinitis may be the common reaction to a number of different environmental agents (e.g. different viruses) and even auto-immunity itself may be genetically heterogenous. Thus, it is reductionist to view all patients as belonging to a homogenous group of either Type 1 or Type 2 disease.

We, therefore, suggest that before the question of suitable control subjects is addressed, attention be paid to collecting homogenous affected populations. In Type 1 diabetes this may be possible by concentrating on sub-groups with certain auto-antibody specificities or distinctive clinical time course. In Type 2 diabetes, we have previously shown that associations with RFLP (restriction fragment length polymorphism) markers linked to the GLUT2 gene were only seen in those subjects with affected first degree relatives [4]. It may be that this sub-group was particularly homogenous for GLUT2 defects. More recently, Groop et al. [5] reported that an association between Type 2 diabetes and a glycogen synthetase polymorphism was also more pronounced in subjects with a positive family history for the disease.

The important point to remember is that these studies are *case/control* studies. Ideally each case should be individually matched to several controls. The current practice of collecting a heterogenous group of affected subjects and comparing them with a group of non-affected individuals from the same ethnic group is far from satisfactory.

Individual matching of cases to controls will require more careful analysis of the clinical, metabolic and immune profiles of subjects. In Cardiff a large cohort of patients with newly-presenting and untreated Type 2 diabetes have been the subject of intensive metabolic study for many years. We hope that this approach will allow the recruitment of a relatively homogenous population of diabetic patients to which unaffected control subjects can be individually matched with respect not only to ethnic origin but also to parameters of insulin secretion and resistance.

Yours sincerely,

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Response from the authors

Dear Sir,

We certainly agree with Alcolado and colleagues that *affected* subjects (with either Type 1 or Type 2 diabetes) should be homogenous as much as possible in terms of disease pathogenetic characteristics. However, in our article [1] we addressed more the aspect of *control* subjects for case/control analysis of susceptibility to diabetes because, for the latter group, there is no general consensus on which type of individuals should be selected.

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