Letters to the Editor

Metabolic control and progression of diabetic nephropathy

Dear Sir,

We read with interest the paper by Dr. Nyberg and her colleagues [1] asserting an impact of metabolic control upon the progression of clinical diabetic nephropathy. In fact what they showed was an association between glycosylated haemoglobin and the rate of decline of glomerular filtration rate (GFR) in a group of 18 patients with impaired renal function due to diabetic nephropathy. Dr. Nyberg does not need reminding, we feel sure, that correlation does not imply cause (though it may be compatible with it). Nor need we remind her that we were very careful in the choice of words in our earlier paper when we concluded that we had been unable to establish a statistically significant effect of improved control upon the rate of decline of renal function in our own small group of patients. We certainly did not claim to have excluded one.

In that study [2] in the conventionally treated control group the rate of decline of GFR also changed from 14.9 to 10.9 ml/min per year between run in and experimental period. These values were not statistically significantly different from the rates of GFR fall in the insulin pump treated group, respectively, at 16.2 and 8.3 ml/min per year. Moreover, in a more recent randomised, controlled study in intermittently proteinuric Type 1 (insulin-dependent) diabetic patients [3] we were also unable to show an effect of correction of hypergly-

caemia on the rate of decline of GFR. This changed from 12 ml/min per year during the run in period to 9.6 ml/min per year during the intensified treatment period, a variation indistinguishable from the changes found in the matched control group treated with conventional insulin therapy. We can properly be criticised for the inadequate statistical power of our studies, but in these controlled, though small, settings we failed to find evidence in favour of Dr. Nyberg's belief.

Dr. Nyberg et al. go to great length explaining that the specific HbA_{1c} fraction was measured; their assay nevertheless does not remove carbamylated haemoglobin which, in these patients, must contribute, to a lesser or greater extent, to the actual HbA_{1c} value. Interestingly the one thing that Dr. Nyberg et al. did not enter into their stepwise multiple logistic analysis was plasma urea. To have found no correlation between GFR and HbA_{1c} at exit from the study does not prove that different plasma urea levels (perhaps higher in those patients whose GFR was falling faster) did not contribute to the statistical significance of the correlation between glycosylated haemoglobin and the slope of GFR change. It would be interesting to see the results of this further analysis.

We have reviewed 24 proteinuric (total urinary protein excretion from 0.5 to 17 g, mean 3 g/day) Type 1 diabetic patients (17 M, 7 F)

Table 1. Glomerular filtration rate (GFR) at entry to and exit from study. Slope of GFR change, mean glycosylated haemoglobin (HbA_{1c}), mean standing and supine mean arterial pressure (MAP) in 24 Type 1 (insulin-dependent) diabetic patients with diabetic nephropathy

Patient no.	GFR at entry (ml/min per 1.73 m ²)	GFR at exit (ml/min per 1.73 m ²)	Linear slope coefficient (ml/min per month)	Mean HbA _{1c} (%)	Mean standing MAP (mmHg)	Mean supine MAP (mmHg)
1	132	116	-0.6	10.2	95	99
2	44	24	-0.6	9.6	108	115
3	51	25	-0.3	9.9	96	103
4	78	55	-2.2	10.6	106	113
5	77	44	-0.7	11.0	92	102
6	90	71	-0.5	7.5	104	104
7	37	24	-1.0	8.9	118	118
8	111	118	+0.2	10.2	88	83
9	99	82	-0.7	7.8	90	105
10	95	68	-0.9	9.5	102	102
11	185	149	-0.3	9.7	81	83
12	58	29	-0.5	9.4	111	108
13	36	33	-0.2	7.5	96	97
14	116	68	-0.4	8.9	103	104
15	34	28	-0.5	11.4	108	108
16	70	25	-0.8	11.1	101	102
17	112	52	-1.2	10.6	103	106
18	93	51	-0.7	9.9	97	97
19	27	18	-0.3	11.8	96	121
20	95	66	-0.5	8.0	114	119
21	69	48	-0.9	10.8	103	109
22	87	55	-1.0	10.2	106	108
23	12	5	-0.1	12.2	74	119
24	55	12	-0.5	10.0	104	110
Mean	78	53	-0.6	9.9	100	106
SD	39	36	0.5	1.3	10	9.8

aged between 29 and 65 years (mean 45 years) with duration of diabetes ranging between 13 and 50 years (mean 25 years) who, for all intents and purposes, were comparable to Dr. Nyberg's patients. Follow-up in these patients varied from 12 to 92 months (mean 43 months) with measurements of 51 CrEDTA GFR, glycosylated haemoglobin, supine and standing blood pressure (together with a number of other variables) ranging from 3 to 15 (average 8) times. No planned dietary changes occurred during this time. Table 1 shows GFR at entry to and exit from the study, the slope of GFR estimates (calculated on all points for each patient), mean glycosylated haemoglobin and mean arterial pressure (MAP) standing and supine, over the observation period. We found no significant correlation between the slope of GFR change and mean glycosylated haemoglobin ($r = -0.08$). The correlation with supine MAP was $r = -0.31$ (NS) and that with standing MAP was $r = -0.45$ ($p < 0.05$). Thus by using the same method of analysis chosen by Dr. Nyberg et al. we would come (as many other workers have) to the conclusion that arterial pressure is a more significant correlate of the rate of change of GFR in diabetic nephropathy than blood glucose. We feel however that this form of analysis is fraught with problems.

One can really draw no more certain conclusions from the association of "spontaneous" levels of control achieved (particularly when variables which fluctuate over time, such as glycosylated haemoglobin and arterial pressure, are averaged for calculation purposes neglecting the time/change interaction) than one could from the many older studies of "control and complications" based upon the finding of increased frequency of abnormality in diabetic patients with some selected record of glycaemia. While it is likely that these reports indicate some relationship between hyperglycaemia and specific diabetic complications generally, one cannot conclude that the relationship is causal (in either direction) and one certainly cannot exclude the operation of other 'third' factors in determining the association. In the case of diabetic kidney disease, rapidly worsening renal failure may itself cause increased difficulty in controlling the diabetes. It is our experience that fear of increased hypoglycaemia risk is a powerful reason for some nephropathic patients to relax their efforts at tight control. The only way out of this confusion of cause, effect and "third factor association" is to take control of the putative determinants (glycaemia in this case) in a properly designed, randomised comparison of the effects of two deliberately selected glycaemic levels. Without this, it is too fatally easy to be seduced by supposition, to see in an innocent data collection a relationship that fits one's hopes and preconceptions. It is revealing of Dr. Nyberg and her colleagues' attitude that in their discussion metabolic control is recognised as only a *second* risk factor in clinical diabetic nephropathy. Second to what? Presumably blood pressure even though their study provides no support whatsoever for the view that arterial pressure is a prime risk factor. Perhaps Dr. Nyberg and her colleagues just believe that it must be so.

Yours sincerely,

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References

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Response from the authors

Dear Sir,

Thank you for giving us the opportunity to comment on the criticism raised by Viberti et al. against our paper [1].

It seems that Dr. Viberti and his colleagues are upset about the results we obtained in our prospective study and the fact that we considered them relevant. Perhaps this explains why they have missed some of the points we made.

We have not disputed that hypertension is a risk-factor for progression of renal insufficiency in diabetic nephropathy. On the contrary, we accept, as Dr. Viberti now does, the work of others on this subject. However, during antihypertensive therapy, the effect of blood pressure might be eliminated. What we discussed in our paper is whether this was the case in our patients. If the blood pressure level is high enough to correlate to the glomerular filtration rate (GFR) decline, as is the case with the patients now presented by Viberti et al., this should preferably be corrected for when a second factor, like HbA_{1c} is considered.

The new data presented by Dr. Viberti et al. illustrate some further problems. The patients are very heterogeneous with regard to GFR. A linear fall towards uraemia cannot be anticipated from levels within or above the normal range. The observation time ranges from one to almost eight years. During this time, blood pressure and glycosylated hemoglobin were recorded about twice a year. This leaves much room for changes in policy and for unrecorded events. The patient material is by no means comparable with ours.

Dr. Viberti and his colleagues do not accept the evidence we produced that glycosylated haemoglobin is a valid measure of glucose control in subjects with reduced GFR, at least as long as they are not frankly uraemic. Nevertheless, they have themselves recorded HbA_{1c} in their nephropathic patients since 1979 and now report the values in support of their own belief. When discussing these data, they even mention blood glucose as a synonym.

In spite of their critical attitude towards our study model, they suggest that we enter plasma urea in the stepwise multiple regression analysis. As plasma urea is strongly dependent on the GFR level as well as on the protein intake, any correlation between plasma urea and GFR fall rate - which is our dependent variable - would be impossible to interpret unless these other variables were also entered. Five variables are far too many for 18 patients.

However, as the question has been raised, we want to report that there was no correlation between serum urea (mean of 7 values per patient) and GFR fall rate ($r = 0.14$) or between serum urea and HbA_{1c} (mean values) during follow-up ($r = 0.04$).

We agree that a properly designed randomised trial with two carefully selected levels of glycaemic control sounds perfect. However, it would certainly be fraught with problems. How, for instance, would the glycaemic level be measured? What arguments should one use to convince a subject with tight control to loosen it and how should better control be obtained in those who do not manage to reach their assigned level?

As for Dr. Viberti's and his colleagues' study on the same subject, they agree that it has an inadequate statistical power.

We believe that the degree of metabolic control has an impact on the progression of renal insufficiency in diabetic nephropathy and we have good reason to do so.

Yours sincerely,

G. Nyberg

References

1. Nyberg G, Blohmé G, Nordén G (1987) Impact of metabolic control on progression of clinical diabetic nephropathy. *Diabetologia* 30: 82-86

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