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Letters to the editor

Glomerular hyperfiltration as a risk factor for diabetic nephropathy: Five-year report of a prospective study

Dear Sir,

While an increased glomerular filtration rate (GFR) is a well recognised feature of early Type 1 (insulin-dependent) diabetes in humans [1, 2] its significance as a risk factor for the later development of overt diabetic nephropathy remains controversial [3–5]. We would like to report the results of the first five-year follow-up assessment of a prospective, case controlled study of glomerular hyperfiltration in clinically non-proteinuric, non-hypertensive (untreated arterial pressure $< {}^{160}/_{95}$ mmHg), Type 1 (insulin-dependent) diabetic patients.

Twenty-six patients were identified as having a GFR above the normal range for our laboratory (83–135 ml·min^{-1}·1.73 m^{-2}) during a screening programme conducted between October 1981 and July 1983. Each was individually matched for age, sex and duration of diabetes with a normofiltering patient randomly selected from the same population. Twenty-five of the matched pairs were available for investigation approximately five years later (hyperfiltering patients {20 male; 5 female}, mean initial age 29 (17–49) years, duration of diabetes 8 (1–19) years; normofiltering patients {20 male; 5 female}, 30 (17–48) and 8 (2–18) years). The mean follow-up interval was 56 months. The study was approved by the Ethical Committee of Guy's Hospital.

Patients were admitted to a Metabolic Ward the evening preceding the study and fasted from 22.00 hours. On the morning of the study height and weight were recorded and blood was taken for HbA_1 (Corning gel electrophoresis), plasma urea and creatinine (multichannel auto analyser, Hitachi, BCL, Lewes, UK). Arterial blood pressure was measured with a standard mercury sphygmomanometer, to the nearest 2 mmHg, in the dominant arm after at least 10 min rest in the supine position. Patients had their usual morning insulin injection 30 min before their breakfast and GFR determination by the single injection technique for ^{51}CrEDTA with 11 point sampling [6] commenced one hour later. A 24 h urine sample (culture negative) was collected for measurement of urinary albumin excretion rate (AER) by radioimmunoassay. Results are expressed as mean (or geometric mean) and 95% confidence intervals unless otherwise stated.

Median (range) initial GFR in the hyperfiltering group was 147 (136–196) ml·min^{-1}·1.73 m^{-2} and at follow up 121 (94–176) ml·min^{-1}·1.73 m^{-2} ($p < 0.01$), falling in 22 (into the normofiltering range in 18) and rising in 3. Initial GFR in the normofiltering group was 116 (93–132) ml·min^{-1}·1.73 m^{-2} and at follow up 112 (57–139) ml·min^{-1}·1.73 m^{-2}, ($p < 0.001$), having fallen in 20 (to below the normal range in 2) and risen in 5 in one case into the hyperfiltering range (Fig. 1). Average rate of change of GFR was −0.46 (−0.32 to −0.60) ml·min^{-1}·month^{-1} in the hyperfiltering group, significantly greater than in the normofiltering group; −0.17 (−0.09 to −0.25) ml·min^{-1}·month^{-1} ($p < 0.005$). Rate of fall of GFR was positively though weakly correlated with initial GFR in the hyperfiltering group only ($r = 0.39$, $p < 0.05$), in neither group was GFR associated with initial AER or arterial pressure levels. Initial and follow-up HbA_1 did not differ significantly between the two groups but fell significantly in each group over the study period (Hyperfiltering patients 9.6 (8.8–10.4) vs 8.8 (8.1–9.4)%, $p < 0.05$; normofiltering patients 10.3 (9.5–11.2) vs 8.5 (7.9–9.1)%, $p < 0.001$). Changes in HbA_1 did not correlate with changes in GFR in either group. On average mean blood pressure and AER remained similar in both groups (mean arterial pressure: hyperfiltering patients 88 (84–92) vs 90 (86–95) mmHg; normofiltering patients 92 (87–97) vs 95 (91–100) mmHg: AER 9.7 (8.7–10.7) vs 8.3 (7.6–9.1) μg/min; 7.1 (6.6–7.7) vs 9.8 (8.9–10.7) μg/min). Rate of fall of GFR was not correlated to increase in AER or in mean arterial pressure in hyperfiltering patients. At screening AER was elevated (> 30 μg/min) in 3 hyperfiltering and in 2 normofiltering patients. At follow-up 2 of the hyperfiltering and both normofiltering patients continued to have elevated values and in addition two other initially normoalbuminuric normofiltering patients showed a rise in AER above 30 μg/min. Mean arterial pressure was higher in those normofiltering patients who were or became microalbuminuric than in those who remained normoalbuminuric, both initially 107 (103–110) vs 89 (84–91) mmHg and at follow-up 107 (101–111) vs 93 (88–98) mmHg, $p < 0.05$.

Our prospective case control study suggests that glomerular hyperfiltration per se, over a five-year interval does not predict the subsequent development of either incipient or overt nephropathy as indicated by elevation of albumin excretion rate or blood pressure. GFR fell in both groups during the follow-up interval but significantly faster in the hyperfiltering group. The differences in the rate of fall

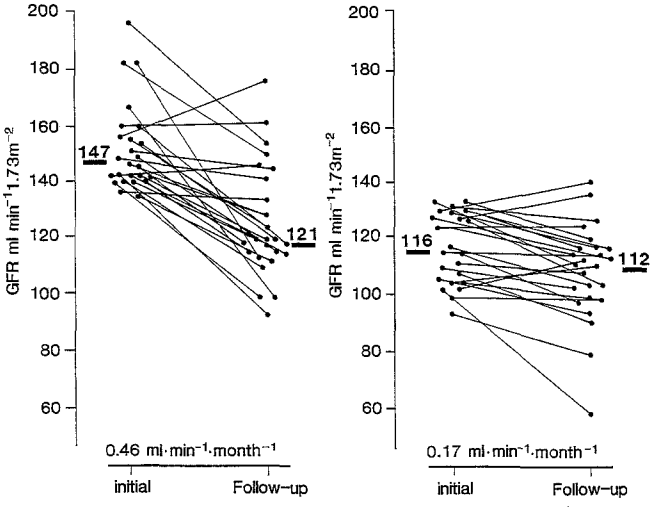

Fig. 1. Initial and follow-up glomerular filtration rates (GFR) in 25 hyperfiltering *(left panel)* and 25 normofiltering *(right panel)* Type 1 (insulin-dependent) diabetic patients. Horizontal bars indicate median values. Mean rate of fall is given as ml·min^{-1}·month^{-1}

cannot be ascribed to different changes in glycaemic control which improved similarly in the two groups during the follow-up interval. The significance of the increased rate of loss of GFR within or above the normal range in the hyperfiltering patients remains uncertain; whether it will continue through and below the normal range will be determined by continuation of our study.

Yours sincerely,
S. L. Jones, M. J. Wiseman and G. C. Viberti

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Glucose infusion rates during euglycaemic clamps do not precisely reflect action profiles of subcutaneously injected insulin

Dear Sir,

In a recent paper Heinemann et al. [1] report on their attempts to quantify the action profile of insulin analogues which were presumed to be absorbed faster than human insulin. They conclude from their results that the analogues B9Asp/B27Glu and B10Asp exhibit "significantly faster onset of action as compared to regular insulin". However, due to a major drawback of the experimental design, this conclusion does not appear to be justified.

According to the experimental protocol employed in this study [2], plasma glucose was clamped in healthy subjects at 5 mmol/l by means of a Biostator-GCIIS for 8 h, while insulin was infused intravenously at 0.1 mU/kg × min. Thus, plasma insulin concentrations of about 10 mU/l were attained [2]. Insulin preparations to be tested were injected subcutaneously 90 min after starting the clamp procedure. Increases of glucose infusion rates above basal are interpreted by the authors as representing the action profile of the insulin under study.

From the literature it can easily be inferred [3], that an experimental protocol like this will result in only partly suppressed endogenous glucose production under both basal and post-injection periods. Moreover, due to variations of plasma insulin concentrations, it must be assumed, that the suppression of endogenous glucose production will change during the experiment at variable degrees. In addition, it cannot be presumed that insulin analogues and unmodified insulin inhibit endogenous glucose production as well as endogenous insulin secretion to the same extent. The glucose infusion rates necessary for maintaining euglycaemia are at best rough estimations for glucose metabolism, but they by no means reflect it quantitatively. Therefore, glucose infusion rates are not valid measures for comparing the action profiles of different insulins, especially when the values obtained differ by a small amount as in the present study.

In our opinion, the study design has to be modified (e. g. by inclusion of glucose turnover measurements) before definitive conclusions regarding faster absorption of these insulin analogues can be drawn.

Yours sincerely,
W. Kerner, F. S. Keck and E. F. Pfeiffer

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Response from the authors

Dear Sir,

Kerner et al. are wrong in suggesting that the determination of glucose infusion rates during a euglycaemic clamp as used by us in studies on insulin pharmacokinetics [1] is an invalid measure for characterizing insulin action profiles. They are correct in noting that hepatic glucose production is not completely suppressed according to our experimental protocol and that it may indeed vary during the experiment due to changes in circulating insulin concentrations. In fact, a further decrease of an initially incompletely suppressed hepatic glucose production rate is to be expected if bioactive insulin preparations are subcutaneously injected during the experimental protocol, as it represents part of the physiological in vivo response to exogenous insulin. The aim of our experimental protocol was to measure the overall effect of bioavailable insulin, i. e. the biological action of different insulin preparations after being absorbed into the circulation following its subcutaneous injection. In this context, a complete suppression of basal hepatic glucose production is neither necessary nor desireable, since peripheral glucose utilization rates would steadily increase during prolonged clamp studies at higher basal insulin concentrations [2]. In our euglycaemic clamp studies on insulin pharmacokinetics, we have therefore routinely used basal low dose insulin infusions in order to suppress endogenous insulin secretion which might otherwise be inadvertently stimulated during glucose infusions. Any additional information concerning absolute rates of hepatic glucose production and peripheral glucose metabolism appear to be of minor relevance. It is up to the personal judgement of Kerner et al. to describe a twofold increase of insulin action