# Early Worsening of Diabetic Nephropathy in Type 2 Diabetes After Rapid Improvement in Chronic Severe Hyperglycemia

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In people with chronically severe hyperglycemia, a paradoxical deterioration of microvascular complications may occur if glycemic control is improved very rapidly. This "early worsening" is well documented for retinopathy (1) and painful neuropathy (2), but not nephropathy.

We describe three men and one woman (ages 38–61 years) who presented with marked hyperglycemia. Type 2 diabetes had not previously been recognized in three cases, but the presence of retinopathy and signs of neuropathy indicated diabetes of at least 5 years' duration. In the fourth case, diabetes had been diagnosed 6 years earlier, but the subject had declined treatment. In case 1, diabetes was recognized coincident with Hodgkin lymphoma, which was successfully treated with nonnephrotoxic chemotherapy. In case 2, diabetes was recognized at presentation with sepsis and acute kidney injury that rapidly improved with volume repletion and antibiotic treatment. None were smokers, had cardiovascular disease, or had a family history of renal disease. At presentation mean values were as follows: BMI 25.0 kg/m$^2$, A1C 118 mmol/mol (12.9%), and estimated glomerular filtration rate (eGFR) 70 mL/min/1.73 m$^2$. One subject was treated with insulin from diagnosis; one took insulin for 3 months, then transferred to oral hypoglycemic agents; and two were treated only with oral hypoglycemics (metformin and/or a sulfonylurea in each case). By 6 months the mean A1C had fallen to 48 mmol/mol (5.5%) and stayed at this level over the next 2–3 years (Fig. 1*A*).

Renal function was assessed by the eGFR, and renal blood flow was examined by Duplex ultrasound of the main renal arteries, with measurement of the renal arterial resistive index (RI), which assesses intrarenal arterial compliance and vascular resistance. The renal sediment was inactive in all cases. Albuminuria increased in all four subjects between 6 and 12 months but thereafter remained stable (Fig. 1*B*). Antihypertensive treatment with cilazapril or losartan was started between 0 and 23 months (Fig. 1*C*). Diuretic therapy was started at diagnosis in one subject, and in two others it was added at 18 and 24 months, respectively. There was no significant change in blood pressure during the first 6 months.

In all four subjects, eGFR fell by 23–35 mL/min/1.73 m$^2$ in the first year, with a slower rate of loss thereafter, stabilizing at a mean 52% of pretreatment levels by 2–3 years (Fig. 1*C*). Expressed as an annualized rate of decline, the greatest loss occurred in the first 6 months (mean 41 mL/min/year) (Fig. 1*D*). Renal ultrasonography was essentially normal, and there was no evidence of renal arterial disease. The RI, measured a median 3 years after starting treatment, was in the normal or intermediate range (mean 0.72; range 0.64–0.79). Serial photography showed progression of retinopathy with the development of cotton wool spots. Three needed treatment with retinal laser and intravitreous bevacizumab injections. All had vibration sense measurements >98th centile, indicating peripheral neuropathy.

The subacute time course and the magnitude of the irreversible loss of eGFR we observed does not fit with that seen in established diabetic nephropathy or acute kidney injury, or in major vascular occlusion. The pathophysiology is unknown, but reduced glomerular filtration pressure consequent upon the abrupt lowering of intravascular osmotic pressure is likely to be critical. It is interesting that despite chronic hyperglycemia none of the four subjects had a high eGFR at baseline, suggesting that renal function was, to some extent, already compromised. There was no clear temporal relationship with the introduction of cilazapril or losartan and none became hypotensive, but in three cases these drugs could have reduced filtration pressure further. In the early worsening of retinopathy, cotton wool spots, which result from arteriolar occlusion at the borders of large ischemic areas, are a dominant feature (1,3). In the case of neuropathy,



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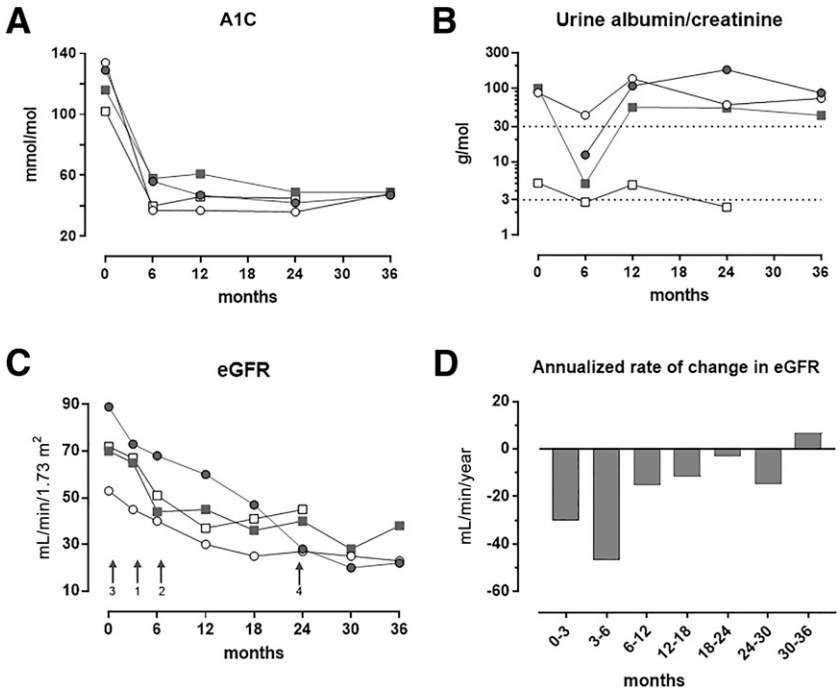


**Figure 1**—*A*: Individual measures of glycated hemoglobin (A1C). *B*: Individual measures of urine albumin/creatinine ratio (logarithmic scale); dotted lines indicate albuminuria categories (normal, <3 g/mol; microalbuminuria, 3–30 g/mol; macroalbuminuria, >30 g/mol). *C*: Individual measures of eGFR. Filled circles: subject 1 (60-year-old woman); open circles: subject 2 (53-year-old man); filled squares: subject 3 (38-year-old man); open squares: subject 4 (61-year-old man). Arrows indicate the time antihypertensive treatment was started in each subject (numbered). *D*: Mean annualized rate of change in eGFR in various time periods. All times are measured from the initiation of treatment for severe hyperglycemia.

reduced microvascular perfusion may induce apoptosis because of ischemia and/or glucose deprivation (4). The renal RI values were in the range commonly found in type 2 diabetes (5), consistent with the hypothesis that hemodynamic changes in the renal microvascular circulation, superimposed on diabetic glomerular disease, were key to the pathogenesis of early worsening.

The phenomenon that we observed could represent the nephropathy equivalent to the early worsening of retinopathy and neuropathy following rapid changes in glycemic control. That this effect does not seem to have been reported previously may be because such exceptionally profound and rapid change in glycemic control is not often attained or sustained and possibly that autoregulation in the renal microvasculature is more resilient than in the retina or vasa nervorum. We agree with the advice that rapid reduction of severe chronic hyperglycemia should be avoided, particularly if there is evidence of existing microvascular disease.

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