Reversible Hyperkalemia at the Initiation of ACE Inhibitors in a Young Diabetic Patient With Latent Hyporeninemic Hypoaldosteronism

Hyporeninemic hypoaldosteronism syndrome is found in patients with diabetes of long duration and/or with renal failure and is an important cause of isolated hyperkalemia (1). Although certainly underestimated, this syndrome has important clinical repercussions, as illustrated by this case report.

A 23-year-old man with type I diabetes for 17 years was hospitalized for treatment of severe diabetic complications. This patient had proliferative retinopathy, diabetic nephropathy with proteinuria, hypertension with blood pressure of 160/110 mmHg, and peripheral and autonomic neuropathy. Serum chemistry showed the following values: potassium, 4.3 mmol/l; creatinine, 106 μmol/l. Treatment with an ACE inhibitor was initiated with a dose of 1.25 mg Ramipril. Five days later, two biological controls revealed a rise in serum potassium levels to 5.7 mmol/l without concomitant elevation of creatinine, which returned to normal values 3 days after the discontinuation of the treatment. Hyporeninemic hypoaldosteronism was suspected 1 month later from low active plasma renin (APR) and plasma aldosterone (PA) values: resting, 5.3 pg/ml (normal, 6.6–9.0) and 51 pmol/l (normal, 40–85); standing, 7 pg/ml (normal, 17.4–25.2) and 105 pmol/l (normal, 17.4–25.2), respectively. The administration of 1.25 mg Ramipril induced a decrease in both resting and standing APR and PA values 18 h later. This patient was normotensive with calcium-channel blockers and had a constant salt ingestion (100 mmol/day).

This case report illustrates the close relationships between ACE inhibitors and the renin aldosterone system through the decrease of circulating angiotensin II levels (2). Hyperkalemia is a known side effect of such treatments in azotemic patients (3). However, since ACE inhibitors have been proposed as a first choice of treatment of incipient and overt diabetic nephropathy, our observation raises the necessity to monitor plasma potassium levels shortly after the initiation of such therapy in young diabetic patients without severe renal failure. An underlying hyporeninemic hypoaldosteronism syndrome may predispose such patients to dangerous hyperkalemia, which makes such treatment inadvisable.

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Metformin Potentiates Glucose-Stimulated Insulin Secretion

There is general agreement that in diabetic patients the biguanide drug metformin exerts its therapeutic action without affecting insulin release (1). In response to oral glucose, peripheral C-peptide and insulin levels are unchanged, after metformin treatment (2). However, because plasma glucose levels are lower after metformin therapy, the unchanged insulin concentrations might mean that the secretion of the hormone is actually increased on a relative basis.

We studied 11 patients with NIDDM, 5 men and 6 women aged 58 ± 1.5 years, with BMI of 27 ± 0.8 kg/m^2, glycated hemoglobin (HbA_{1c}) of 7.0 ± 0.6%, basal C-peptide level of 0.7 ± 0.03 nmol/l, and treated with diet alone or diet plus metformin. In a random order, with 5–7 days between each test, patients were given two oral glucose loads, 35 and 50 g, in the form of 50% dextrose solution. Fifteen minutes before the 50 g glucose test, 850 mg oral metformin was given. Pilot experiments had been performed to assess the amounts of glucose to be given, with and without metformin, to obtain similar peripheral venous plasma glucose levels.

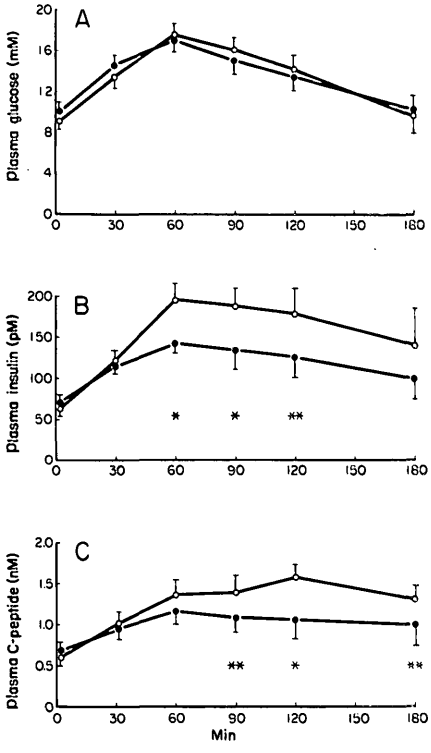

Figure 1—*Plasma glucose (A), insulin (B), and C-peptide (C) concentrations in patients with NIDDM given 35 g oral glucose (●) or 50 g oral glucose plus 850 mg oral metformin (○). *P < 0.05, **P < 0.02.*

In addition, we prepared isolated pancreatic islets from six cadaver donor pancreases (procured through regional Organ Procurement Organizations, with coordination by the National Disease Research Institute) by combining a digestion-filtration technique and a density gradient purification system (3,4). After overnight culture in CMRL 1066 medium at 37°C, the islets were perifused as described (4) to test the effect of 3.7 μg/ml metformin (Laboratory Guidotti, Pisa, Italy) on insulin release at 3.3 and 16.7 mmol/l glucose.

As shown in Fig. 1*A*, patients with NIDDM showed similar peripheral plasma glucose concentrations when receiving either 35 g glucose or 50 g glucose