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.

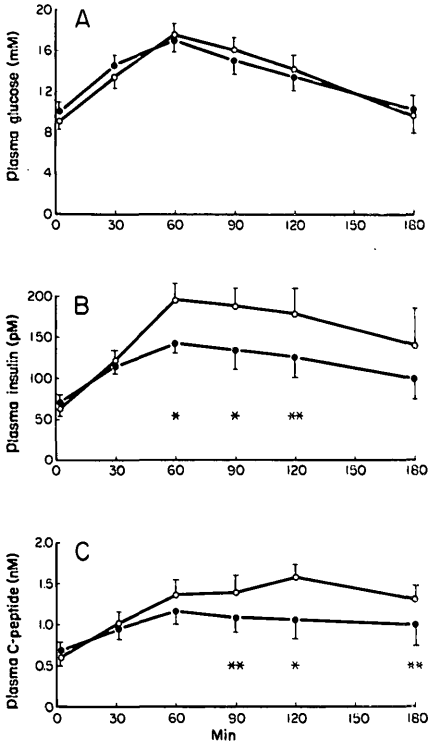

Figure 1—*Plasma glucose (A), insulin (B), and C-peptide (C) concentrations in patients with NIDDM given 35 g oral glucose (●) or 50 g oral glucose plus 850 mg oral metformin (○). *P < 0.05, **P < 0.02.*

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

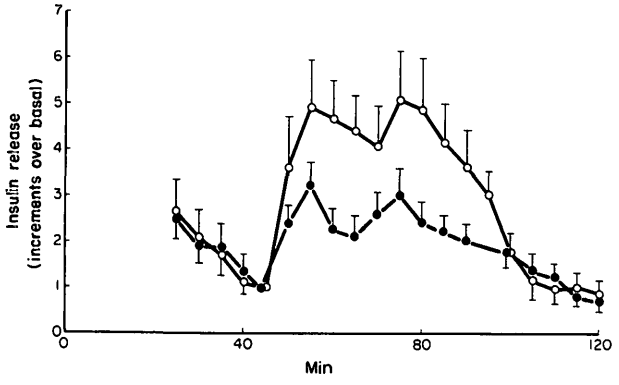

Figure 2—*Insulin release from isolated human islets perifused with different glucose concentrations and without (●) or with (○) the addition of 3.7 μg/ml metformin in the perifusion medium during the 40–80 min period.*

plus 850 mg oral metformin. The areas under the plasma glucose curve were essentially the same: 2,403 ± 155 and 2,498 ± 160 mmol at the low and high (plus metformin) dextrose dose, respectively. Plasma insulin (Fig. 1*B*) and C-peptide (Fig. 1*C*) concentrations rose higher after metformin administration. The areas under the plasma insulin curve were 25,295 ± 4,641 and 33,408 ± 6,327 pmol ($P < 0.01$) after 35 g glucose and 50 g glucose plus metformin, respectively. The values for the plasma C-peptide curves were 16.7 ± 2 and 21.0 ± 3 nmol ($P < 0.01$), respectively, without and with metformin.

In the perifusion experiments performed with 3.3 mmol/l glucose (six replicates), basal insulin release was 24.0 ± 1.4 pmol/l, and the addition of 3.7 μg/ml metformin had no significant effect on hormone output (peak value, 32 ± 8 pmol/l). In the experiments in which after 40 min of perifusion with 3.3 mmol/l glucose the concentration of dextrose was increased to 16.7 mmol/l, either with or without the addition of metformin (five replicates each), peak insulin secretion in the presence of 16.7 mmol/l glucose plus metformin (126 ± 46 pmol/l) was significantly ($P < 0.05$) higher than the peak insulin release from islets from the same pancreases at 16.7 mmol/l glucose without metformin (94 ± 31 pmol/l) (Fig. 2). Total insulin release from islets perifused for 40 min with 16.7 mmol/l glucose plus metformin was 3,640 ± 741 pmol. This value was significantly higher ($P < 0.05$) than that from islets perifused with 16.7 mmol/l glucose without metformin (2,161 ± 438 pmol).

Thus, in our NIDDM patients, after 35 g oral glucose and 50 g oral glucose plus 850 mg oral metformin, similar peripheral plasma glucose concentrations were achieved. Under this condition, a significant increase of plasma insulin and C-peptide levels was found, after metformin dosing. Although increasing doses of oral glucose per se may stimulate greater levels of insulin, possibly by enhancing gastric inhibitory polypeptide (GIP) or other gastrointestinal hormones, significant changes in maximal GIP and insulin levels after oral glucose usually occur when the glucose load increase is at least twofold (5). Conversely, metformin does not cause any significant change in GIP concentrations either fasting or after a test meal (6). Therefore, our results might be explained, at least in part, by an effect of metformin on the β-cell. Indeed, the drug significantly potentiated insulin release from isolated perifused human islets in the presence of 16.7 mmol/l glucose. Since metformin did not affect insulin release at low glucose, this might explain why the drug does not cause hypoglycemia. Although the mechanism(s) by which metformin affects insulin release is not known at this time, our results suggest that oral metformin may potentiate insulin release in patients with NIDDM, given oral glucose, and that this effect is at least in part due to a direct action of the drug on the β-cell.

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Response to Garber

Alan Garber's editorial in *Clinical Diabetes* (1), expressing his depression regarding the failed penetration of the educational message of the American Diabetes Association (ADA) regarding glycemic control, reminded me of