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Enhancement of Fibrinolysis After Insulin Administration in NIDDM

Defective fibrinolysis, which has been associated with an increased risk of thromboembolic disease,[1,2] has been documented in diabetes mellitus and may be relevant to the vascular complications of diabetes.[3,4] Indeed, impaired fibrinolytic responses to venous stasis are more common in diabetic individuals with microangiopathy.[5,6] Depression of fibrinolysis is more closely linked to non-insulin-dependent diabetic (NIDDM) patients,[7–9] and cross-sectional studies have suggested an association of defective fibrinolysis with the use of sulfonylurea drugs.[10,11] These studies have assessed overall fibrinolysis by measurement of the plasma fibrinolytic activity, which reflects mainly the levels of plasminogen activators. Recently, an assay for the Bβ 15-42 fragment of fibrin(ogen), which gives a measure of plasmin-mediated fibrinolysis, has become available and will be a useful tool in estimating changes in fibrinolysis. We have measured a variety of tests of fibrinolysis in a group of sulfonylurea-treated NIDDM patients and monitored the effects of substitution of insulin therapy. The effect on fibrinolysis of such a change in therapy has not previously been reported.

Twenty (15 women, 5 men) C-peptide–positive NIDDM patients of mean age 62 yr (range 51–72 yr), duration of diabetes 7.5 yr (range 1–26 yr), and mean percentage of ideal body weight (Geigy scientific tables) of 103% (range 72–125%) took part in the study. Despite high-dose sulfonylurea administration (glibenclamide 15 mg b.i.d.), the patients developed symptomatic hyperglycemia with constant glycosuria and random clinic capillary glucose values between 270 and 450 mg/dl. They were therefore judged to have secondary failure of sulfonylurea therapy and to require insulin. Five patients had microangiopathy and six had macroangiopathy. Each patient was placed on Lentard M.C. (Novo Industries, Copenhagen, Denmark) highly purified beef/pork lente insulin with dosage adjusted thereafter as clinically indicated. Fasting venous blood was taken at 0, 1, and 3 mo for glycosylated hemoglobin (HbA_1) and assessment of fibrinolysis. HbA_1 was performed by agar gel electrophoresis (Glytrac, Dow Corning Corp., Midland, Missouri). The Bβ 15-42 fragment of fibrin(ogen) was measured by an RIA (IMCO, Stockholm, Sweden) with the spontaneous fibrinolytic activity performed by the lysis area (mm^2) of the euglobulin fraction on fibrin plates.[12] Fibrinogen, plasminogen, and the inhibitors of fibrinolysis, α2 antiplasmin and α2 macroglobulin, were performed as previously described.[12] Statistical comparisons utilized the Wilcoxon matched-pairs rank test.

Table 1 shows an enhancement of fibrinolysis without change in glycemic control, although patients improved symptomatically. This activation of fibrinolysis was seen in patients with and without macro- and microvascular disease. No correlations were noted between HbA_1 and the tests of fibrinolysis and no changes in the other components of the fibrinolytic enzyme system were found. By 3 mo the patients' mean insulin dosage was 42 U (range 28–68 U) with a mean weight gain of 2.6 kg (range −0.5 to 9.5 kg).

We have shown that on stopping sulfonylurea drugs and substituting insulin therapy, improvement of spontaneous fibrinolytic activity occurs. The increased concentration of the Bβ 15-42 fragment indicates increased plasmin-induced lysis of fibrin(ogen). This fibrinolytic enhancement could not be explained by the weight change after insulin therapy, an alteration of glycemic control, and was not influenced by the presence of preexisting vascular disease. It is possible that sulfonylurea therapy has a deleterious effect on fibrinolysis with a rebound improvement in fibrinolytic activity on cessation of such therapy. Prospective assessment of fibrinolysis in a small group of newly diagnosed NIDDM patients placed on sulfonylurea therapy for 1 yr has not shown impairment of fibrinolysis,[9] but this does not exclude a possible effect on fibrinolysis with high dosage and prolonged treatment. If long-term sulfonylurea treatment does indeed lead to impaired fibrinolysis, then it is interesting to speculate whether the high frequency of cardiovascular deaths in sulfonylurea-treated diabetic patients observed in the UGDP study[13] could be linked to depression of fibrinolysis. Alternatively, insulin treatment may stimulate fibrinolysis and there is evidence that insulin has a direct effect on the endothelial cell,[14,15] which is the site of storage of vascular plasminogen activator.

Our preliminary observations indicate that enhancement

TABLE 1
Concentrations of fibrinolytic parameters over the 3 mo of study (mean ± SD, N = 20)

	Time (mo)		
	0	1	3
Fibrinolytic activity (mm^2)	79 ± 20	91 ± 23*	93 ± 22†
Bβ 15-42 (pmol/L)	0.96 ± 0.58	1.31 ± 0.67	1.44 ± 0.66‡
HbA_1 (%)	13.2 ± 2.3	13.1 ± 2.1	12.3 ± 2.1

*$P < 0.05$, †$P < 0.01$, ‡$P < 0.02$.

of fibrinolysis in poorly controlled NIDDM patients occurs when we transfer patients with secondary sulfonylurea failure to insulin treatment. Whether this effect is due to withdrawal of sulfonylurea therapy or a direct effect of insulin is the subject of further study.

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Jejunostomy Feeding in the Management of Gastroparesis Diabeticorum

Gastroparesis diabeticorum is an uncommon, but well-recognized, serious syndrome complicating diabetic autonomic neuropathy.[1,2] It may be asymptomatic in mild and early cases; in more severe cases it may manifest as early satiety, postprandial distension, nausea, abdominal pain, vomiting of undigested material consumed a few hours earlier followed by relief of pain, or the persistent taste of food eaten a day or two before. Because of the severe postprandial symptoms, patients may become severely depressed and significantly reduce the quantity and frequency of food intake. Irregular eating patterns compounded by delayed gastric emptying lead to brittle, uncontrolled diabetes.[3] In recent studies, metoclopramide and domperidone have been shown to increase gastric motility and to be effective as treatments.[4,5] However, clinical efficacy may diminish with time and patients become refractory to the drugs. The results of surgical treatment have been disappointing in most cases. In this comment, we describe the benefits of jejunostomy tube placement with enteral feeding in four patients with type I diabetes mellitus (IDDM) complicated by refractory gastroparesis.

SUBJECTS AND METHODS

Gastroparesis was confirmed in all patients by radionuclide gastric-emptying studies, both liquid ($t_{1/2}$ 6–18 min) and solid ($t_{1/2}$ 21–71 min) meals, and pressure motility recording of activity of the interdigestive myoelectric complexes. A #16 red French Robinson (Davol, Cranston, Rhode Island) feeding tube was placed percutaneously within the jejunum at a site shown to be functionally relatively normal. The external edge of the tube was kept in place by suturing to the skin.

Patient 1. A 35-yr-old white woman (K.F.) with IDDM since the age of 19 yr was admitted in early 1980 with a history of repeated episodes of hypoglycemia and ketoacidosis. She had peripheral neuropathy, mainly sensory, minimal background retinopathy, nephropathy (creatinine clearance 57 ml/min), autonomic neuropathy consisting of pupillary and urinary bladder dysfunction, postural hypotension, and postprandial symptoms of nausea, vomiting, abdominal pain, and bloating. In August 1981, significantly delayed gastric emptying was observed ($t_{1/2}$ > 300 min); however, there was prompt gastric emptying (14 min) of liquids after intravenous (i.v.) metoclopramide and the patient was treated orally with the drug. Symptoms recurred and she was readmitted in October 1982. A gastrointestinal motility study revealed the absence of phase III motility in the stomach and proximal intestine with no response to i.v. domperidone. It was anticipated that the combination of bowel rest and optimized blood glucose control would partially reverse the clinical problem, therefore the patient ingested nothing by mouth and received total parenteral nutrition and i.v. insulin therapy.