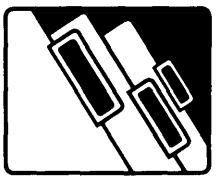
Case Reports



Pathophysiology of Beta Cell Failure After Prolonged Remission of Insulin-dependent Diabetes Mellitus (IDDM)

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The pathophysiology of beta cell failure in IDDM has not been well documented. Islet cell responsiveness (C-peptide and glucagon) to oral glucose (OGTT), intravenous glucose (IVGTT), and arginine infusion was studied sequentially in a 24-yr-old nonobese patient with IDDM in prolonged remission interrupted by an episode of diabetic ketoacidosis and followed by a second transient (6 mo) partial recovery of beta cell function. The earliest abnormality in glucose tolerance was demonstrated with the IVGTT (K = 0.77) although OGTT (F, 101; ½ h, 177; 1 h, 211; 1½ h, 144; and 2 h, 111 mg/dl) and glucagon responses to glucose and arginine were normal. With the development of abnormal OGTT, glucagon failed to suppress with hyperglycemia although basal levels were not elevated. With the development of frank clinical diabetes, C-peptide did not respond to oral or i.v. glucose although stimulation in response to arginine infusion was still possible. Basal glucagon concentrations were now elevated. Thus, the failing beta cell shows a progressive deterioration in its responsiveness to various secretagogues in a sequential manner (i.v. glucose followed by oral glucose and then i.v. arginine). Abnormalities in glucagon secretion can be demonstrated early in the development of abnormal oral glucose tolerance. With more precise elucidation of the etiology of diabetes, it may be possible to intervene therapeutically in diabetic individuals who experience a remission in order to prevent further deterioration in beta cell function. DIABETES CARE 1: 83–87, JANUARY–FEBRUARY 1984.

The recovery of endogenous insulin secretion shortly after the initiation of insulin treatment in newly diagnosed insulin-dependent diabetic individuals (IDDMs) is not an uncommon clinical occurrence. However, the duration of this period of endogenous insulin recovery, often referred to as the "honeymoon" period, is generally short lived (several weeks to months) and is rarely complete. Several early studies[1–8] have examined insulin secretory function during the remission phase although the mechanisms responsible for this phenomenon remain entirely obscure. In addition, the sequential changes in islet cell function presumably responsible for the clinical observations have not been well documented. In this article, we describe a case of diabetes in remission of prolonged duration, interrupted by an episode of characteristic diabetic ketoacidosis followed by a subsequent second transient partial recovery of beta cell function. Pancreatic islet cell responses to oral and i.v. glucose and arginine infusion were studied to document sequentially the pathophysiology of beta cell failure.

CASE REPORT

The patient (W.L.) is a 24-yr-old white man who was well until June 1976 (age 17) when he gradually developed polyuria, polydipsia, and weight loss over a 3-wk period. He was admitted to the intensive care unit of a community hospital in diabetic ketoacidosis. His initial blood work showed a blood glucose of 800 mg/dl; electrolytes Na 136, K 6.5, Cl 95, and CO_2 10 mmol/L, with an arterial pH of 7.03. The urine was strongly positive for ketones with 4+ glucosuria. He was treated with intravenous fluids and insulin and improved over the next several days. An underlying or precipitating cause for his diabetic ketoacidosis was not identified. After several days of diabetes teaching, he was discharged on 36 U NPH insulin daily. In follow-up, he had normal fasting (79–103 mg/dl) and postprandial (73–114 mg/dl) plasma glucose determinations and his urine was always negative for glucosuria.

In the spring of 1980, 4 yr after his initial presentation, his insulin dose was progressively reduced by 4 U/wk to de-

termine if he required exogenous insulin. He remained symptom free with normal plasma glucose off insulin (fasting 96; 2 h postprandial 105 mg/dl) and was admitted to the Clinical Investigation Unit of the Toronto General Hospital for further evaluation. Physical examination was entirely normal. Routine admission biochemistry, hematology, chest X-ray, electrocardiogram, and urinalysis were all normal. His HbA_1 (glycosylated hemoglobin) was 7.1% (normal 6.5–8.5%), T4 11.2 μg/dl, T3 resin uptake 29.3%, TSH 4.2 μU/ml. Thyroid antimicrosomal antibodies were positive at a titer of 1:25,600. The cholesterol was 144 mg/dl, triglycerides 60 mg/dl, HDL cholesterol 44 mg/dl, and LDL cholesterol 87 mg/dl. Beta cell function was evaluated with IVGTT, OGTT, and arginine infusion during this admission and 4 mo after discharge. He was kept off insulin and was asymptomatic until November 1981 (17 mo without insulin and 5 yr since his initial presentation). He then presented with a 2-wk history of polyuria, polydipsia, and weakness that prompted admission to hospital. His blood glucose was elevated at 260 mg/dl; his electrolytes were abnormal: Na 137, K+ 4.2, Cl 104, and CO_2 16 mmol/L. His urine was strongly positive for ketones. Insulin therapy was reinstituted and his fasting plasma glucose ranged between 200 and 300 mg/dl on progressively increasing doses of insulin. He was discharged on 45 U lente insulin daily, which was increased to 58 U lente and 2 U regular insulin each morning. For several weeks after discharge, the patient noted frequent glucosuria, which abated after approximately 1 mo, after which his urines were again consistently negative for glucose and ketones.

In February 1982, he was readmitted to the Clinical Investigation Unit for reevaluation. The patient felt well and physical examination revealed a well-nourished, muscular young man, 175 cm in height and 78 kg in weight. The family history was positive for IDDM in a paternal grandmother and a nephew. There was no family history of thyroid, adrenal, or rheumatoid disease. Both his parents and five siblings, including a twin sister, were nondiabetic. Routine admission laboratory work was again normal. The HbA_1 was slightly elevated at 9.3%, T4 7.9 μg/dl, and T3 resin uptake 29.2%. There was no evidence of diabetic complications. The patient's insulin was discontinued for 5 days with consistently normal fasting glucoses (78–116 mg/dl) and he remained asymptomatic without insulin. Repeat provocative IVGTT, OGTT, and arginine infusion were carried out. The patient was discharged on 6 U lente insulin daily.

His diabetic control continued to be excellent until July 1982 when he lost his job and was under considerable stress. He began to experience polyuria, polydipsia, and nocturia. A blood sugar done as an outpatient was over 300 mg/dl and the patient was readmitted to the Clinical Investigation Unit. Physical examination was unremarkable. Repeat provocative testing was again carried out as per the previous protocol. The HbA_1 was now clearly elevated at 11.2%. The patient was discharged on 18 U lente insulin, which has been increased steadily to 32 U lente and 4 U regular insulin in order to achieve acceptable diabetic control.

METHODS

All studies of islet cell function were carried out on separate days after an overnight fast. The patient was not receiving insulin and his previous diet contained 300 g carbohydrate. Three tests were performed with measurements of plasma glucose, C-peptide, and glucagon as previously described.[9–11] Specifically, glucagon was determined on plasma from venous blood

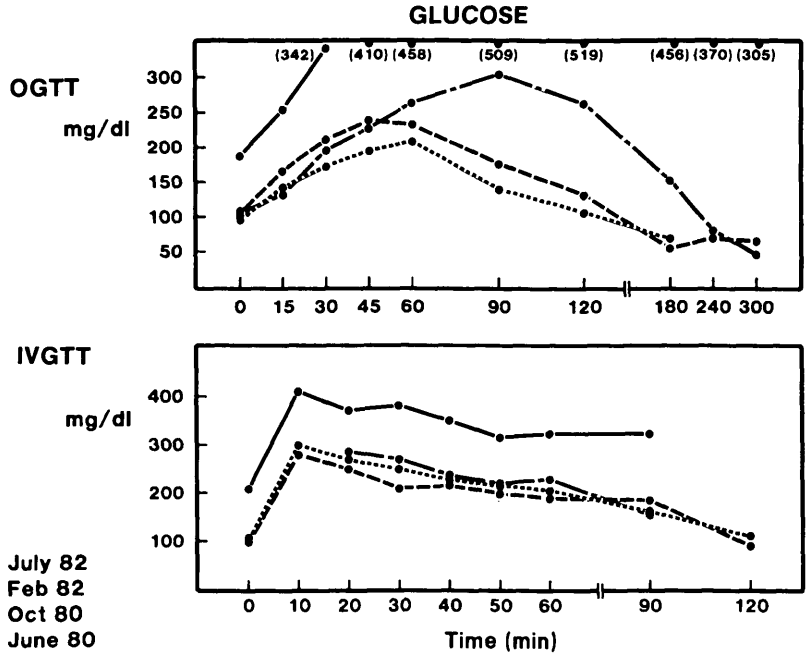

FIG. 1. Oral and i.v. glucose tolerance (plasma glucose) determined sequentially from June 1980 through July 1982.

collected in tubes containing heparin and aprotinin (Trasylol, 10,000 Kallikrein inhibitor U/ml; FBA Pharmaceuticals, New York, New York) using antiserum 30K (obtained from Dr. R. H. Unger, Dallas, Texas), purified pork glucagon standard and ^{125}I-labeled pork glucagon (Novo Research Institute, Copenhagen, Denmark), and a dextran-coated charcoal separation technique. C-peptide was assayed on PEG (polyethylene glycol) extracts using synthetic human C-peptide standard and tracer, and antiserum M 1230 (Novo Research Insitute).

IVGTT. Intravenous glucose was administered as a 50% dextrose solution (0.5 g/kg) over 2–5 min.

OGTT. Glucose (Glucola, 75 g) was given orally over a 10-min period.

Arginine infusion. Arginine (30 g) was administered intravenously over a 30-min period.

RESULTS

Glycemic response to oral and i.v. glucose. The glycemic responses to oral and i.v. glucose are shown in Figure 1. A sequential deterioration in OGTT was seen with initially normal glucose tolerance[12] first becoming mildly abnormal in October 1980 and then profoundly abnormal by July 1982. In contrast, although the IVGTT was abnormal when first examined in June 1980 (K = 0.77) it remained unchanged until July 1982 when marked deterioration occurred (K = 0.23).

C-peptide response to oral and i.v. glucose and arginine. The C-peptide responses to oral and i.v. glucose differed from the response to arginine (Figure 2). As compared with previous studies by Block et al.[13] of normal controls, the basal C-peptide concentration and the response to oral glucose was normal until July 1982. C-peptide increased with i.v. glucose in June and October 1980 and became unresponsive in July 1982. In contrast, C-peptide continued to increase in response to arginine even after the recurrence of clinical diabetes.

Glucagon response to oral and i.v. glucose and arginine. Initially glucagon suppressed in response to OGTT (Figure 3). Basal levels remained unchanged but glucagon failed to suppress when tested in February 1982. Increased basal levels and an apparent paradoxical increase in response to glucose occurred in July 1982. The glucagon response to arginine remained essentially unchanged until July 1982 when basal levels were somewhat elevated and an exaggerated response to arginine was seen.

DISCUSSION

The patient described in this article is of interest for two reasons. First, he is an example of a prolonged remission of diabetes interrupted by diabetic ketoacidosis and followed by a subsequent period of beta cell recovery. Second, since beta cell responsiveness was essentially intact when he was in remission, we were able to study sequentially the pathophysiology of the evolving beta cell failure.

Most patients reported in the literature have experienced remission from weeks to months after the onset of diabetes. While there exists a substantial number whose remission lasted 1–3 yr, long-standing remission is quite rare. Carlstrom and Ingmanson[14] reported a patient initially diagnosed at age 17 whose remission spanned 12 yr and three normal pregnancies. Hines and Kessler[15] described a patient who had been in remission for 10 yr. Peck et al.[16] reported remission of diabetes in a 41-yr-old man who presented in severe diabetic coma. He was followed for 3-yr without evidence of any biochemical relapse. None of the above patients had

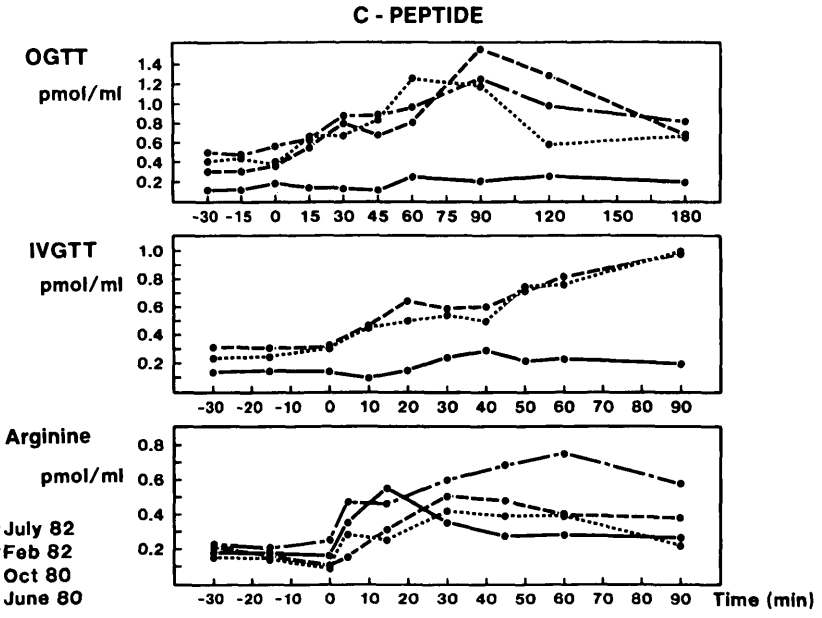

FIG. 2. Response of serum C-peptide to stimulation testing with oral glucose, i.v. glucose, and i.v. arginine from June 1980 through July 1982.

beta cell function evaluated in response to various secretagogues with measurements of insulin or C-peptide.

Our patient is unusual in that his remission only appears to have been recognized 4 yr after he presented in ketoacidosis and a second remission occurred after another episode of ketoacidosis. Although one cannot be certain that he was in remission for the 4-yr period he was treated with insulin, patients who experience a recovery of beta cell function do so in close relationship to the initiation of insulin therapy. The recovery of beta cell function spontaneously after 4 yr of endogenous insulin deficiency of the magnitude seen in type I diabetes would be distinctly unique. This case is similar to a patient described by Genuth[6] who had three episodes of ketoacidosis and two documented remissions over a 5-yr period. The natural history of this type of fluctuating beta cell function is not known. Foucar and Field[17] studied newly diagnosed, ketosis-prone diabetic patients and found that correction of hyperglycemia is followed by a wide range of insulin responses that correlate poorly with eventual outcome. Mirouze et al.[18] compared 12 newly diagnosed IDDMs treated with short-term (5 days) blood glucose control by the artificial beta cell with 28 similar patients treated with conventional insulin therapy. The frequency of "remission" (patients maintained off insulin but on oral agents for 3–14 mo) was significantly greater in the group treated with the artificial beta cell. In contrast, Perlman et al.[19] prospectively studied two groups of newly diagnosed IDDMS. One group was treated with a portable, preprogrammed, open-loop i.v. insulin infusion system for 28–62 days; the other group was treated with conventional insulin therapy. These authors concluded that initial sustained normoglycemia does not result in a prolonged improvement in beta cell function. Thus, it remains unclear whether metabolic normalization can affect newly diagnosed IDDMs.

When first studied, our patient demonstrated a completely normal OGTT[12] and normal C-peptide responses to oral glucose.[13] Although the IVGTT was abnormal, C-peptide was also released in response to this stimulus. In addition, glucagon suppressed and increased physiologically to glucose and arginine, respectively, indicating intact alpha cell function. Although documentation of islet cell secretory capacity has often been incomplete in previously reported cases of remission, normalization of islet cell responsiveness is distinctly uncommon, although discontinuation of insulin therapy is often possible. Recovery of beta cell function as shown by serial glucose tolerance testing has been reported in a patient with diabetic ketoacidosis associated with mumps virus.[20]

The long-term recovery of islet cell function demonstrated by our patient allowed us to document sequentially the evolving pathophysiology of the subsequent development of frank diabetes. In agreement with Srikante et al.[21] the earliest abnormality in beta cell function appeared to be an abnormal response to i.v. glucose. Despite this abnormality, normal beta cell response could still be achieved via the "enteral" pathway of beta cell stimulation by glucose. Alpha cell function was also essentially unaffected. With progression of the islet pathology, oral glucose tolerance deteriorated and glucagon now failed to suppress with hyperglycemia. Subsequently, symptomatic diabetes recurred and the beta cell failed to respond to either oral or i.v. glucose although an increase in C-peptide with arginine could be shown. Glucagon concentrations were now elevated. Thus, the failing beta cell loses its responsiveness to various secretagogues in a sequential manner and abnormalities in glucagon secretion occur in concert with the early abnormalities of glucose tolerance.

The study of patients in remission provides an opportunity to further define the pathophysiology of islet cell dysfunction

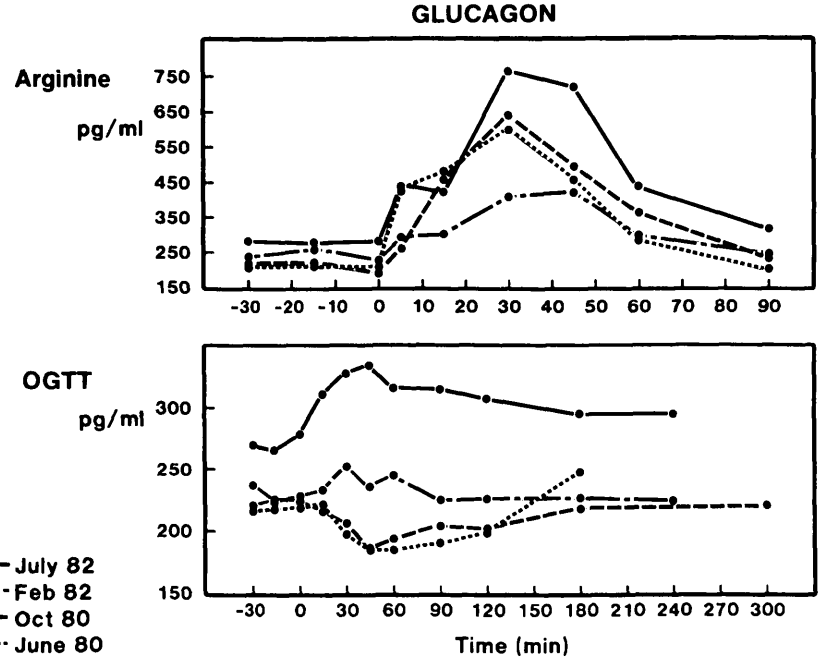

FIG. 3. Glucagon response to oral glucose and i.v. arginine from June 1980 through July 1982.

in diabetes. With more precise elucidation of the etiology of diabetes, specific recommendations with regard to the induction and maintenance of diabetes in remission may be possible.

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