

The Honeymoon Period in Non-Insulin-Dependent Diabetes Mellitus

William J. Crump, MD
Huntsville, Alabama

Dietary management is the cornerstone of care in non-insulin-dependent diabetes mellitus (NIDDM). In adults, partial or complete remissions of hyperglycemia are usually attributed to loss of weight during diet therapy in a previously obese patient.¹ In insulin-dependent diabetes (IDDM), transient remissions are commonly known as the "honeymoon period," and generally continue for weeks to months. The current hypothesis is that early aggressive control of blood glucose levels temporarily remedies the relative beta cell exhaustion and allows for short-term glucose homeostasis without exogenous insulin.² Control of blood glucose without significant weight loss in a nonobese patient may precipitate a remission phase in NIDDM, but such reports are rare.³ The case presented here demonstrates such a remission phase in a lean patient.

CASE REPORT

A 58-year-old man presented for his first visit with a three-week history of weakness, polyuria, polydipsia, polyphagia, and a 12-lb weight loss. He had no history of diabetes mellitus in himself or his family. He smoked one pack of cigarettes a day, did not drink alcohol, and took no regular medications.

Physical examination showed a well-nourished, well-developed man. His height was 6'1", weight 202 lb, blood pressure 116/90 mmHg, heart rate 88 beats per minute, and ear, nose and throat, lung, cardiac, and abdominal examination revealed no abnormalities. A random blood glucose determination was 17.5 mmol/L (316 mg/dL), he had glucosuria (4+), and his urine was negative for ketones.

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From the Family Medicine Program, School of Primary Medical Care, University of Alabama in Huntsville, Huntsville, Alabama. Requests for reprints should be addressed to Dr. William J. Crump, UAH Medical Clinics, 201 Governors Drive, SW, Huntsville, AL 35801.

His ideal body weight was calculated to be 190 to 200 lb, and he was begun on a 2,000-calorie American Diabetes Association diet. At two visits over the next two weeks, he showed a further 4-lb weight loss and complete resolution of all symptoms. His fasting blood glucose levels were 15.5 to 15.7 mmol/L (279 to 282 mg/dL), and two-hour postprandial levels were 19.6 to 20.8 mmol/L (353 to 375 mg/dL). Six weeks after initial presentation his weight was 196 lb, and his fasting blood glucose was 5.5 mmol/L (99 mg/dL) with postprandial level of 7.3 mmol/L (132 mg/dL) (Figure 1). Three months into his illness his weight was 198 lb, and his fasting blood glucose measured 5.4 mmol/L (98 mg/dL) and postprandial 5.6 mmol/L (100 mg/dL). Ten months after presentation, his postprandial blood glucose level was 5.6 mmol/L (100 mg/dL), and he began a more liberal approach to his diet. He did not return again until 23 months after presentation, when he again had a three-week history of polyuria and polydipsia. At this time, his postprandial blood glucose level was 15.3 mmol/L (275 mg/dL), weight was unchanged, and he was again placed on a 2,000-calorie diet. His blood glucose levels continued in the range of 15.3 to 16.7 mmol/L (275 to 300 mg/dL) despite the calorie restriction, and at his request, an oral hypoglycemic was begun with subsequent good control of blood glucose levels.

DISCUSSION

This nonobese patient demonstrated a prolonged remission of hyperglycemia after calorie restriction. In IDDM factors predicting remission include advanced age, male sex, and mild initial metabolic derangement.² This remission is thought to be dependent on a functional recovery of the beta cell,⁴ which has been shown to coincide with return of insulin release in response to a glucose load.⁵ The duration of the remission phase is inversely correlated with hemoglobin A_{1C} at the time of diagnosis,⁶ supporting the concept that decreasing islet cell demand may result in a longer remission.

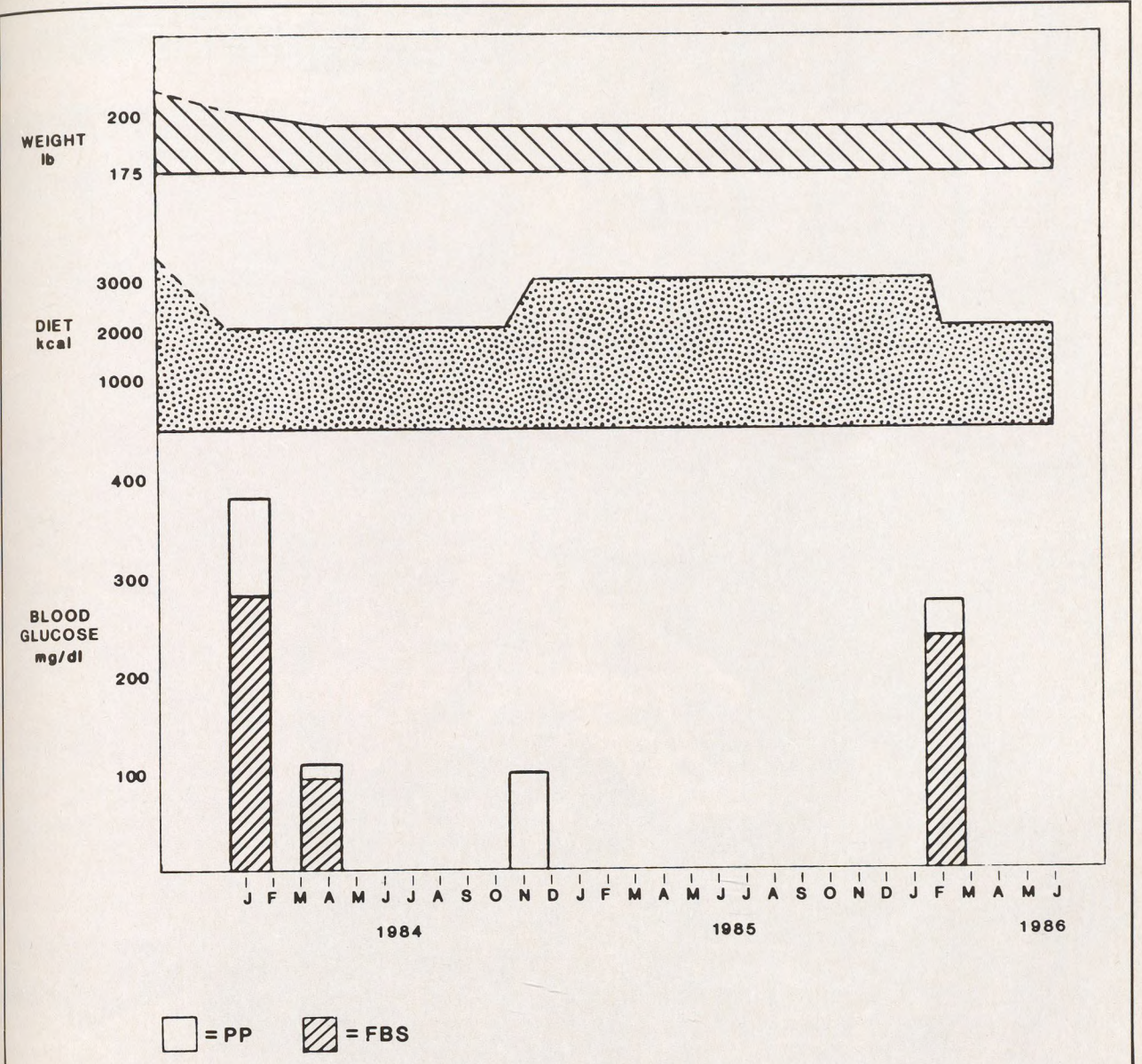


Figure 1. Patient's clinical data. PP, postprandial blood glucose levels; FBS, fasting blood glucose levels

Pirart and Lauvaux⁷ reported a large series of remissions in 1971. Of the 280 cases summarized, 76 showed no weight change and 7 actually gained weight. Presence of ketonuria was not found to be predictive of a remission in these patients. Wall et al⁸ reported in 1973 that 80 percent of obese diabetics in their series of 200 had their blood glucose levels controlled by carbohydrate restriction and 80 percent of these achieved control without weight loss. Another group of 118 NIDDM patients managed with diet only showed an increase in stimulated insulin levels that correlated with the degree of weight loss during

treatment, but the mean weight loss was only 5.1 kg (11.2 lb).⁹ These authors suggested an analogy of remission with Starling's law of the heart. As weight or glucose load increases the load on the pancreas, the organ enters a failure curve, which can be partially reversed by reducing the load with weight loss or dietary management. In the patient discussed here, only a heavy caloric load can be identified as a precipitant for beta cell insufficiency, which abated temporarily with calorie restriction. Secondary causes of hyperglycemia including epidermoid neoplasms,¹⁰ thyroid disease, pheochromocytoma, and ad-

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Reference:

1. Sachs R, Frank M, Fishman SK: Overview of clinical experience with glipizide, in *Glipizide: A Worldwide Review*. Princeton, NJ, Excerpta Medica, 1984, pp 163-172.

GLUCOTROL® (glipizide) Tablets

Brief Summary of Prescribing Information

INDICATIONS AND USAGE: GLUCOTROL is indicated as an adjunct to diet for the control of hyperglycemia in patients with non-insulin-dependent diabetes mellitus (NIDDM, type II) after an adequate trial of dietary therapy has proved unsatisfactory.

CONTRAINDICATIONS: GLUCOTROL is contraindicated in patients with known hypersensitivity to the drug or with diabetic ketoacidosis, with or without coma, which should be treated with insulin.

SPECIAL WARNING ON INCREASED RISK OF CARDIOVASCULAR MORTALITY: The administration of oral hypoglycemic drugs has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin. This warning is based on the study conducted by the University Group Diabetes Program (UGDP), a long-term prospective clinical trial designed to evaluate the effectiveness of glucose-lowering drugs in preventing or delaying vascular complications in patients with non-insulin-dependent diabetes. The study involved 823 patients who were randomly assigned to one of four treatment groups (*Diabetes* 19, supp. 2:747-830, 1970).

UGDP reported that patients treated for 5 to 8 years with diet plus a fixed dose of tolbutamide (1.5 grams per day) had a rate of cardiovascular mortality approximately 2-1/2 times that of patients treated with diet alone. A significant increase in total mortality was not observed, but the use of tolbutamide was discontinued based on the increase in cardiovascular mortality, thus limiting the opportunity for the study to show an increase in overall mortality. Despite controversy regarding the interpretation of these results, the findings of the UGDP study provide an adequate basis for this warning. The patient should be informed of the potential risks and advantages of GLUCOTROL and of alternative modes of therapy.

Although only one drug in the sulfonylurea class (tolbutamide) was included in this study, it is prudent from a safety standpoint to consider that this warning may also apply to other oral hypoglycemic drugs in this class, in view of their close similarities in mode of action and chemical structure.

PRECAUTIONS: Renal and Hepatic Disease: The metabolism and excretion of GLUCOTROL may be slowed in patients with impaired renal and/or hepatic function. Hypoglycemia may be prolonged in such patients should it occur.

Hypoglycemia: All sulfonylureas are capable of producing severe hypoglycemia. Proper patient selection, dosage and instructions are important to avoid hypoglycemia. Renal or hepatic insufficiency may increase the risk of hypoglycemic reactions. Elderly, debilitated, or malnourished patients and those with adrenal or pituitary insufficiency are particularly susceptible to the hypoglycemic action of glucose-lowering drugs. Hypoglycemia may be difficult to recognize in the elderly or people taking beta-adrenergic blocking drugs. Hypoglycemia is more likely to occur when caloric intake is deficient, after severe or prolonged exercise, when alcohol is ingested, or when more than one glucose-lowering drug is used.

Loss of Control of Blood Glucose: A loss of control may occur in diabetic patients exposed to stress such as fever, trauma, infection or surgery. It may then be necessary to discontinue GLUCOTROL and administer insulin.

Laboratory Tests: Blood and urine glucose should be monitored periodically. Measurement of glycosylated hemoglobin may be useful.

Information for Patients: Patients should be informed of the potential risks and advantages of GLUCOTROL, of alternative modes of therapy, as well as the importance of adhering to dietary instructions, of a regular exercise program, and of regular testing of urine and/or blood glucose. The risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients and responsible family members. Primary and secondary failure should also be explained.

Drug Interactions: The hypoglycemic action of sulfonylureas may be potentiated by certain drugs including non-steroidal anti-inflammatory agents and other drugs that are highly protein bound, salicylates, sulfonamides, chloramphenicol, probenecid, coumarins, monoamine oxidase inhibitors, and beta adrenergic blocking agents. *In vitro* studies indicate that GLUCOTROL binds differently than tolbutamide and does not interact with salicylate or dicumarol. However, caution must be exercised in extrapolating these findings to a clinical situation. Certain drugs tend to produce hypoglycemia and may lead to loss of control, including the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. A potential interaction between oral miconazole and oral hypoglycemic agents leading to severe hypoglycemia has been reported. Whether this interaction also occurs with the intravenous, topical, or vaginal preparations of miconazole is not known.

Carcinogenesis, Mutagenesis, Impairment of Fertility: A 20-month study in rats and an 18-month study in mice at doses up to 75 times the maximum human dose revealed no evidence of drug-related carcinogenicity. Bacterial and *in vivo* mutagenicity tests were uniformly negative. Studies in rats of both sexes at doses up to 75 times the human dose showed no effects on fertility.

Pregnancy: Pregnancy Category C: GLUCOTROL (glipizide) was found to be mildly fetotoxic in rat reproductive studies at all dose levels (5-50 mg/kg). This fetotoxicity has been similarly noted with other sulfonylureas, such as tolbutamide and tolazamide. The effect is perinatal and believed to be directly related to the pharmacologic (hypoglycemic) action of GLUCOTROL. In studies in rats and rabbits no teratogenic effects were found. There are no adequate and well-controlled studies in pregnant women. GLUCOTROL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Because recent information suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities, many experts recommend that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible.

Nonteratogenic Effects: Prolonged severe hypoglycemia has been reported in neonates born to mothers who were receiving a sulfonylurea drug at the time of delivery. This has been reported more frequently with the use of agents with prolonged half-lives. GLUCOTROL should be discontinued at least one month before the expected delivery date.

Nursing Mothers: Since some sulfonylurea drugs are known to be excreted in human milk, insulin therapy should be considered if nursing is to be continued.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: In controlled studies, the frequency of serious adverse reactions reported was very low. Of 702 patients, 11.8% reported adverse reactions and in only 1.5% was GLUCOTROL discontinued.

Hypoglycemia: See PRECAUTIONS and OVERDOSAGE sections.

Gastrointestinal: Gastrointestinal disturbances, the most common, were reported with the following approximate incidence: nausea and diarrhea, one in 70; constipation and gastralgia, one in 100. They appear to be dose-related and may disappear on division or reduction of dosage. Cholestatic jaundice may occur rarely with sulfonylureas; GLUCOTROL should be discontinued if this occurs.

Dermatologic: Allergic skin reactions including erythema, morbilliform or maculopapular eruptions, urticaria, pruritus, and eczema have been reported in about one in 70 patients. These may be transient and may disappear despite continued use of GLUCOTROL; if skin reactions persist, the drug should be discontinued. Porphyria cutanea tarda and photosensitivity reactions have been reported with sulfonylureas.

Hematologic: Leukopenia, agranulocytosis, thrombocytopenia, hemolytic anemia, aplastic anemia, and pancytopenia have been reported with sulfonylureas.

Metabolic: Hepatic porphyria and disulfiram-like alcohol reactions have been reported with sulfonylureas. Clinical experience to date has shown that GLUCOTROL has an extremely low incidence of disulfiram-like reactions.

Endocrine Reactions: Cases of hyponatremia and the syndrome of inappropriate antidiuretic hormone (SIADH) secretion have been reported with this and other sulfonylureas.

Miscellaneous: Dizziness, drowsiness, and headache have each been reported in about one in fifty patients treated with GLUCOTROL. They are usually transient and seldom require discontinuance of therapy.

OVERDOSAGE: Overdosage of sulfonylureas including GLUCOTROL can produce hypoglycemia. If hypoglycemic coma is diagnosed or suspected, the patient should be given a rapid intravenous injection of concentrated (50%) glucose solution. This should be followed by a continuous infusion of a more dilute (10%) glucose solution at a rate that will maintain the blood glucose at a level above 100 mg/dL. Patients should be closely monitored for a minimum of 24 to 48 hours since hypoglycemia may recur after apparent clinical recovery. Clearance of GLUCOTROL from plasma would be prolonged in persons with liver disease. Because of the extensive protein binding of GLUCOTROL (glipizide), dialysis is unlikely to be of benefit.

DOSE AND ADMINISTRATION: There is no fixed dosage regimen for the management of diabetes mellitus with GLUCOTROL; in general, it should be given approximately 30 minutes before a meal to achieve the greatest reduction in postprandial hyperglycemia.

Initial Dose: The recommended starting dose is 5 mg before breakfast. Geriatric patients or those with liver disease may be started on 2.5 mg. Dosage adjustments should ordinarily be in increments of 2.5-5 mg, as determined by blood glucose response. At least several days should elapse between titration steps.

Maximum Dose: The maximum recommended total daily dose is 40 mg.

Maintenance: Some patients may be effectively controlled on a once-a-day regimen, while others show better response with divided dosing. Total daily doses above 15 mg should ordinarily be divided.

HOW SUPPLIED: GLUCOTROL is available as white, dye-free, scored diamond-shaped tablets imprinted as follows: 5 mg tablet—Pfizer 411 (NDC 5 mg 0049-4110-66) Bottles of 100; 10 mg tablet—Pfizer 412 (NDC 10 mg 0049-4120-66) Bottles of 100.

CAUTION: Federal law prohibits dispensing without prescription.

More detailed professional information available on request.

DIABETES HONEYMOON PERIOD

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renal cortical tumor,¹¹ are occasionally associated with apparent remissions, none of which were present in this patient.

In summary, a temporary return of blood glucose control with caloric restriction is relatively common in obese patients with NIDDM, even in the absence of weight reduction. This "honeymoon phase" is unusual in lean patients with NIDDM. The case reported here supports the concept of a heavy caloric load as a precipitant in beta cell insufficiency in the nonobese patient.

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