Special Comment
Meticulous Control of Diabetes: Benefits, Risks, and Precautions

ROGER H. UNGER

Meticulous metabolic management of diabetes has become a feasible therapeutic option now being offered to increasing numbers of diabetics in the hope of delaying or preventing diabetic complications. This hope, while still untested by rigorous clinical trials, is nevertheless supported by a considerable body of scientific and clinical data (see ref. 1 for a review) and could well represent the first truly significant therapeutic advance since the discovery of insulin. Recently, however, several reports of unexpected deaths have occurred in patients "tightly" controlled with open-loop insulin delivery devices. At least some of these deaths are believed to have been directly or indirectly attributable to hypoglycemia. These reports, together with new understanding of the hormonal and metabolic lesions in treated and untreated type I diabetes, have raised legitimate questions as to the safety of efforts to normalize glycemia, whether by continuous subcutaneous insulin infusion or by multiple injections. In this review, the potential long-term benefits of meticulous glucoregulation will be weighed against the short-term risks, particularly the risk of hypoglycemic brain damage, and guidelines will be proposed in the hope of reducing the risk-benefit ratio of such regimens to an absolute minimum.

POTENTIAL BENEFITS OF METICULOUS CONTROL (TABLE 1)

SHORT-TERM BENEFITS

The potential short-term benefits of normalizing the plasma glucose throughout the day include subjective well-being, less frequent catabolic crises resulting from underinsulinization, and (perhaps) less frequent infectious complications. Occasionally, treatment with continuous subcutaneous insulin infusion (CSII) may provide greater stability in a patient who had been difficult to regulate by conventional means.

LONG-TERM BENEFITS

Prevention of diabetic complications. The hope that diabetic vascular complications will be prevented by glycemic normalization is based in part on the fact that while thickening of muscle capillary basement membranes may occur in "prediabetics" in the absence of overt hyperglycemia,[2,3] progression from that subtle electromicroscopic abnormality to overt microvascular disease seems to require the presence of the metabolic abnormalities of diabetes.* On the other hand, many diabetics tolerate decades of poor metabolic control without developing clinically detectable diabetic complications. These two seemingly conflicting facts are reconciled by assuming that the metabolic derangements of diabetes are necessary for the development of clinically detectable consequences of microangiopathy, but that individual susceptibility to the detrimental effects of the metabolic derangements varies considerably, possibly on genetic grounds. Until the determinant (or determinants) of susceptibility has been identified, correction of the metabolic disturbance constitutes the only potential prophylactic approach available.

While proof that long-term correction of the metabolic disturbance will prevent end-stage diabetic complications is lacking, there seems at first glance to be no justifiable reason to withhold a therapeutic option that requires no new untested drug but merely a more careful matching of the insulin dose to the daily glucose profile. However, if a regimen of meticulous control were to impose upon the diabetic patient serious risks in excess of those encountered with conventional therapy, it could not then be justified (see below).

Reversal of complications. While prevention of diabetic complications by meticulous metabolic control is a justifiable hope, reversal of end-stage diabetic microangiopathy

From the Veterans Administration Medical Center and the University of Texas Health Science Center, Dallas, Texas.
Address reprint requests to Dr. Roger H. Unger, University of Texas Health Science Center, 5323 Harry Hines Boulevard, Dallas, Texas 75235.
Received for publication 9 March 1982.

* None of the rare case reports of Kimmelsteil-Wilson's disease in the absence of hyperglycemia have been adequately substantiated.

TABLE 1
Benefits of meticulous metabolic control of diabetes mellitus

Short-term benefits
Subjective well-being
Less frequent catabolic crises
Greater stability of plasma glucose in certain brittle patients
Normal growth in children
Prevention of maternal-fetal complications in diabetic pregnancy
Less frequent infectious complications (?)
Long-term benefit
Hope of prevention or delay of diabetic complications

is not, despite evidence that it improved retinal and renal function.[4] Efforts of reversal should not be attempted except under the most rigid experimental conditions. End-stage diabetic nephropathy must be regarded as an absolute contraindication to rigorous control until after renal transplantation (see below).

POTENTIAL RISKS OF METICULOUS CONTROL (TABLE 2)

The long-term risks of regimens intended to maintain constant normoglycemia are obviously still unknown. The potential serious short-term risks of such regimens are listed in Table 2.

Accelerated diabetic retinopathy. Acceleration of diabetic retinopathy has been reported during treatment by CSII in patients that had previously been poorly controlled.[5] Conventionally managed patients probably have far less frequent funduscopic examinations than patients on a new form of treatment, making it possible that the observation of worsening retinopathy on pump therapy is simply the consequence of more careful scrutiny of the fundi. Nonetheless, institution of meticulous control in such patients warrants more frequent funduscopic examinations, with fundal photographs, if possible, to detect early signs of rapidly advancing retinopathy. If such a phenomenon proves real, the mechanism may involve the rise in somatomedin levels associated with metabolic amelioration.[6]

Hypoglycemic encephalopathy. The most serious and most preventable complication of rigorous measures of control, and the major focus of this review, is hypoglycemic encephalopathy leading to permanent brain damage or death. As of February 1982, twelve unexpected deaths had occurred in the estimated 4000–5000 patients now receiving insulin by continuous subcutaneous infusion.[7] In at least six cases, hypoglycemia was suspected as being a cause or contributory factor in the death. Hypoglycemic encephalopathy has been a recognized risk since the introduction of insulin therapy, but whether it is more common in meticulously controlled patients than with conventional therapeutic regimens is unknown. Since it is a presumably preventable tragedy, its occurrence, however infrequent, is never acceptable. In view of the above reports and the apparent rarity of mechanical pump failures,[8] it is imperative that a search for nonmechanical flaws in CSII and other types of aggressive regimes be made.

TABLE 2
Risks of meticulous control of diabetes mellitus

Short-term risks
Possible worsening of retinopathy in patients previously in poor state of control (?)
Hypoglycemic encephalopathy
Local abscesses at site of indwelling needle
Long-term risks
Unknown

CONTRIBUTING FACTORS TO HYPOGLYCEMIA (TABLE 3)

Unrealistic therapeutic goals and inappropriate selection of candidates for therapy, combined with hormonal and metabolic vulnerability of type I diabetics to severe hypoglycemia, may heighten the risk of serious hypoglycemia in aggressively treated patients.

Unrealistic therapeutic goals. Avoidance of hyperglycemia, rather than avoidance of hypoglycemia, is generally stressed as the first priority of meticulous control. This quest for "normalization," rather than "near-normalization," of glucose profiles increases the risk of the regimen without certainty of enhanced benefit. Overt microangiopathic complications rarely develop in less than 6 yr in type II Pima patients with postglucose load hyperglycemia below 250 mg/dl,[9] raising the possibility that there may be a zone of metabolic control above the normal range in which an optimal risk-benefit ratio may be found.

In particular, a normal fasting glucose level may be a dangerous therapeutic objective because blood glucose levels often rise substantially between midnight and early morning, the so-called "dawn phenomenon."[10] A normal glucose concentration at 7 a.m. may, therefore, be a sign of dangerous hypoglycemia 4–6 h earlier. Yet, to achieve fasting normoglycemia, some insulin delivery devices are programmed to deliver increased quantities of insulin during sleep, i.e., they are designed to eliminate the dawn phenomenon, which may be an important protection against nocturnal hypoglycemia. Until there is unequivocal evidence of benefits sufficient to justify the potentially great risk of hypoglycemia in normoglycemic regimens, it seems prudent to suggest that near-normalization of a glycemic profiles (<130 mg/dl fasting, <180 mg/dl postprandially) rather than normalization is a preferable therapeutic target.

Inappropriate selection of patients. The risks of meticulous control are enhanced by inappropriate choice of patients. "Inappropriate" may mean that the potential benefits are too low and/or the potential risks are too high. Inasmuch as the hoped-for long-term objective of idealized treatment is the prevention of complications that require 5 yr or more to develop, patients whose life expectancy is limited by advanced age or other life-shortening disease obviously will not be potential beneficiaries of such therapy. Unless there is some important short-term justification, they should be excluded as candidates for meticulous control. The same criterion for exclusion applies to patients with advanced complications of diabetes, as there is no basis for hoping that end-stage microangiopathic lesions can be reversed by meticulous control. Ideal candidates for meticulous control

TABLE 3
Candidates for meticulous control

Diabetics in otherwise good health and without hypoglycemic risk factors or advanced diabetic complications
Pregnant diabetic mothers beginning before conception, irrespective of their state of health
Diabetics following renal transplantation irrespective of their general health

are listed in Table 3. The largest eligible group consists of diabetic subjects in otherwise good health and without advanced diabetic complications in whom maintenance of health is the primary goal of treatment. In diabetic pregnancy, meticulous control is strongly indicated, irrespective of the patient's state of health prior to conception, to minimize fetal morbidity and mortality. It is also indicated immediately after renal transplantation in patients with Kimmelsteil-Wilson disease, irrespective of other health problems. The objective of therapy in this situation is to maintain normal function of the transplanted kidney.

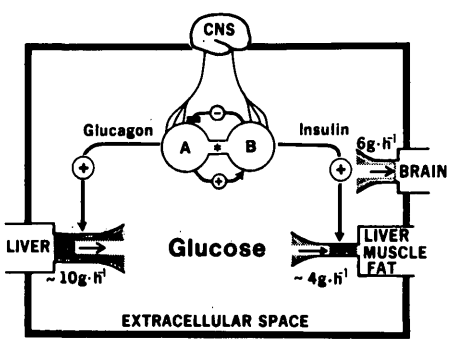
Hormonal factors. The metabolically "normalized" type I diabetic exhibits hormonal dysfunctions that explain the high risk of severe hypoglycemia.

The nondiabetic has a virtually foolproof defense against hypoglycemia, which guarantees the continuous delivery of glucose to the brain. The key component in this "guaranteed" fuel delivery system is the normal islet cell response to a declining arterial glucose concentration, namely, a decline in insulin secretion coupled with a reciprocal rise in glucagon release. Because the fall in insulin mediates the rise in glucagon,[11] thus combining a decrease in glucose utilization with an increase in hepatic glycogenolysis and gluconeogenesis, it is most uncommon for any physiologically occuring perturbation to produce hypoglycemia (Figure 1A).

In type I diabetes, the normal relationship between B- and A-cells is totally disrupted[12] by the paucity of B-cells. In suboptimally insulinized type I diabetes (Figure 1B), oversecretion of glucagon results from the lack of insulin,[13] the A-cells behaving as if they were "blind" to the hyperglycemia. The importance of glucagon-mediated glucose production is emphasized by the fact that hyperglycemia can be reduced in the absence of insulin by blocking either glucagon secretion[14] or glucagon action.[15] When insulin is administered to such patients, it inhibits glucagon secretion,

FIGURE 1A. The normal insulin-glucagon relationship in the basal state. The A- and B-cells, joined by gap junctions (asterisk), are influenced by the levels of circulating nutrients and hormonal signals within the extracellular space, and by neurotransmitted signals from the central nervous system (CNS). There is, in addition, a positive-negative feedback relationship in which glucagon stimulates the B-cell and insulin inhibits the A-cell. Through appropriately coordinated secretion of insulin and glucagon, glucose production by the liver is maintained in constant equality with total glucose utilization by the brain and by insulin-mediated tissues (liver, muscle, and fat) both in the basal state and during perturbations of this equilibrium. For example, if the glucose load declines for any reason, insulin secretion immediately decreases, reducing insulin-mediated glucose utilization while enhancing glucagon secretion and thereby increasing hepatic glucose production. This provides a virtually foolproof failsafe against hypoglycemia.

A.



B.

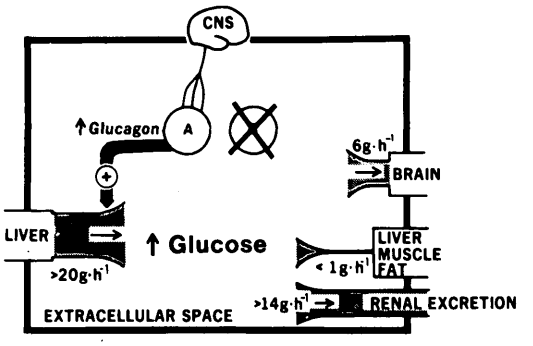


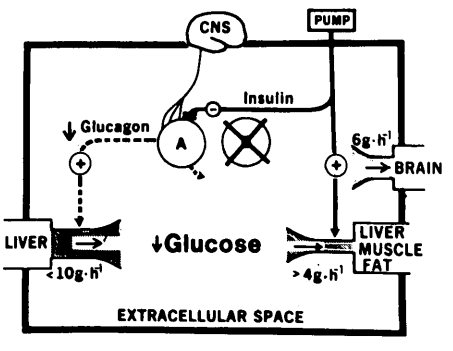
FIGURE 1B. Untreated type I diabetes: the deficiency of insulin lowers insulin-mediated glucose utilization by liver, muscle, and fat, and releases glucagon secretion from inhibition. The resulting unregulated hyperglucagonemia maintains hepatic glucose production in excess of glucose utilization, and glycosuria results.

thereby reducing simultaneously hepatic overproduction of glucose and increasing peripheral glucose uptake. Glucose levels, therefore, decline, but in the insulin-treated diabetic patient, release of insulin from the subcutaneous injection site is, of course, not reduced by a declining glucose level; insulin-mediated glucose utilization remains increased and glucagon and glucagon-mediated glucose production remain suppressed despite impending hypoglycemia[16,17] (Figure 1C). Fortunately, however, in many patients "back-up" protection is provided by a brisk epinephrine and norepinephrine response to a declining glucose level,[17] and this mechanism can maintain or restore normoglycemia (Figure 2).

On the other hand, if the catecholamine "failsafe" against hypoglycemia is obtunded by autonomic neuropathy or adrenergic blockade, the patient becomes hormonally defenseless against hypoglycemia. More worrisome is the report of Boden and co-workers[18] of the case of an insulin-requiring diabetic patient with no clinical evidence of autonomic neuropathy who developed hypoglycemic brain damage consequent to failure of glucagon and cate-

FIGURE 1C. Type I diabetes treated by CSII pump: constant rate replacement of insulin restores glucose utilization by liver, muscle, and fat to normal and suppresses glucagon secretion. However, insulin release is not subject to inhibition by a falling glucose level, thereby eliminating the major failsafe against hypoglycemia, i.e., the declining insulin release as plasma glucose levels fall. The insulin not only maintains glucose utilization in the face of impending hypoglycemia, but maintains suppression of glucagon despite hypoglycemia, thereby preventing the increase in hepatic glucose production required to prevent or correct hypoglycemia. (Adapted from N. Engl. J. Med. *304*:1518–1524, 1981 with permission).

C.



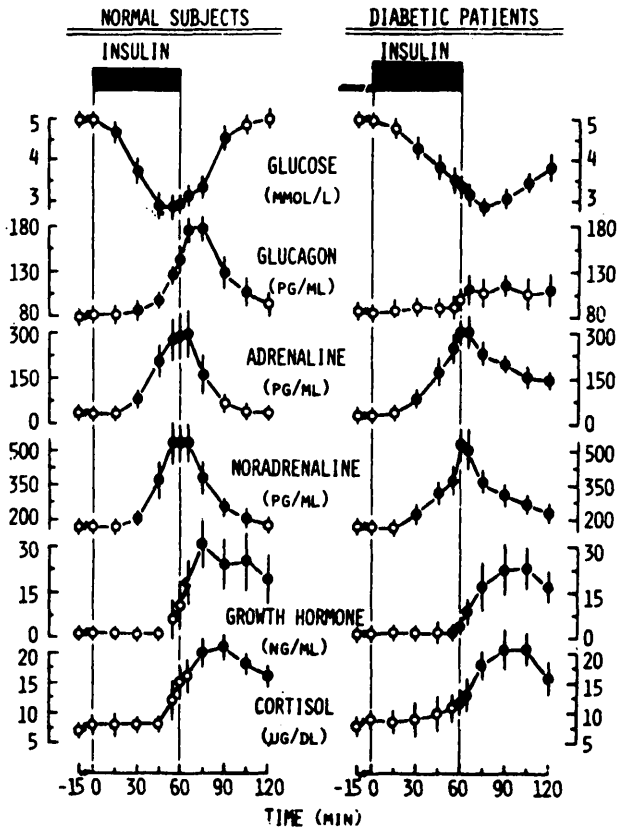


FIGURE 2. The counterregulatory response to insulin-induced hypoglycemia in normal subjects and in diabetic patients. The diabetic patients fail to exhibit a normal glucagon response to hypoglycemia, but in these subjects, in contrast to the patient of Boden et al.,[16] the adrenaline, noradrenaline, growth hormone, and cortisol responses are intact. (Reprinted from Bolli et al. with permission of Diabetologia).

cholamine release after insulin-induced hypoglycemia. This was a selective defect in the counterregulatory hormone response to hypoglycemia, since both the glucagon response to arginine and the catecholamine response to exercise were normal. Idiopathic loss of hormonal defenses against hypoglycemia could represent a previously unrecognized syndrome within the diabetic population.

Metabolic factors. Finally, other metabolic consequences of meticulous control may influence the impact of hypoglycemia on cerebral function. For example, one would predict that the levels of ketones and free fatty acids would be severely depressed during tight control of glycemia by the "clamping effect" of continuous subcutaneous infusion of insulin. The neurologic impact of a given level of hypoglycemia would be expected to be greater if the level of ketones, the alternative cerebral fuel, were kept low by a reduction in circulating free fatty acids, the substrate for ketogenesis. Additionally, continuous reduction in the levels of glucose-sparing fuels and glucogenic substrates could increase the propensity for sudden and severe hypoglycemia, especially during exercise. These possible metabolic consequences of euglycemic clamping by continuous insulin infusion have not yet been tested. Nor is it known if such possible risk factors are greater than with the more erratic control patterns often seen with conventional insulin administration.

In summary, the type I diabetic subject may lack the normal hormonal and metabolic protection against hypoglycemia found in the nondiabetic for the following reasons: (1) inability of a falling glucose level to reduce insulin release; (2) failure of glucagon secretion to rise during a decline in glucose because of continued suppression by the insulin; (3) insulin-induced reduction in the levels of other substrates; and (4) the failure in some patients of the catecholamine response to hypoglycemia, either because of autonomic neuropathy, adrenergic blocking agents, or the idiopathic syndrome described by Boden et al.[18]

Biochemically vulnerable patients are protected only by their subjective awareness of impending hypoglycemia, followed by intake of carbohydrate. During sleep this protection is, of course, inoperative. Unless they are awakened by the episode, there is no possibility of food intake and there may be no one to assist them. The sleeping hours are, therefore, the time of maximal danger.

RECOMMENDATIONS FOR REDUCING THE RISK-BENEFIT RATIO

Modification of therapeutic goals. By permitting mild fasting hyperglycemia of up to ~130 mg/dl† and viewing a 7 a.m. level below 80 mg/dl as a possible sign of predawn hypoglycemia, one should be able to reduce the nocturnal risk. The patient should be trained to regard the prevention of hypoglycemia as the highest priority of the self-care program. Self-monitoring of glucose levels at 2 or 3 a.m. should be encouraged if 7 a.m. levels are below 80 mg/dl. Artificial insulin delivery devices programmed to increase the basal rate in the predawn period should be avoided. Perhaps such devices can be programmed to reduce transiently insulin delivery between midnight and dawn or to deliver glucagon with the insulin during the dangerous hours of sleep. Obviously, the ultimate goal would be a hypoglycemic sensor or alarm that would allow interruption of insulin infusion.

Stringent exclusion of inappropriate patients. The hoped-for goal of meticulous control is the prevention of complications that require from 5 to 20 yr to appear. It makes little sense, therefore, to select patients with a life expectancy that is less than ~5–10 yr. This would exclude elderly patients, or patients who already have severe diabetic nephropathy or any other life-shortening disorder. In particular, patients with cerebrovascular or coronary artery disease should be rejected because of the potentially lethal effects of hypoglycemia. Patients with enhanced sensitivity to insulin because of renal failure, hypophysectomy, adrenal insufficiency, β-adrenergic blockade, autonomic neuropathy, or the syndrome of Boden et al.[18] are obviously not suitable candidates. Evaluation of the counterregulatory hormone responses to insulin-induced hypoglycemia may provide a useful means of excluding patients at highest risk. Finally, individuals who have psychiatric disturbances or alcohol or drug habits or who do not exhibit the required level of reliability and intelligence to understand and implement the principles of diabetic self-care should be excluded.

Intensive training in self-care. Meticulously controlled patients must understand fully all the techniques involved in

† Breakfast is the meal which tends to produce the highest postprandial hyperglycemia. It may be necessary, therefore, to shift most of the breakfast carbohydrate and calories to later in the day and/or to increase the prebreakfast dose of regular insulin so as to minimize the deleterious effects of a fasting hyperglycemia on the rest of the daily blood glucose profile.

their care, the potential risks of treatment, and how to prevent them. This requires a period of intensive instruction best provided in specialized diabetes centers. In particular, patients should be carefully trained to make appropriate precautionary adjustments to prevent hypoglycemia during sleep and during physical exercise. A continuing surveillance program should be designed to assure the patient's safety on a day-to-day basis. Unless these safeguards can be provided, meticulous control regimens in their present form may well entail short-term risks that outweigh their hoped-for long-term benefits.

FINAL NOTE

The foregoing is a best-guess assessment of a rapidly changing area of therapy and is based on anecdotal evidence, theory, and physiologic and clinical intuition. It should not be construed as an attack upon efforts to maintain meticulous metabolic control in diabetes, but is intended rather to call attention to potentially preventable risks of such efforts. The principal short-term risk of meticulous control, as currently applied, may well be hypoglycemic encephalopathy, the consequence of unnecessarily aggressive attempts to normalize glucose profiles in patients who may lack the normal hormonal and metabolic defenses against hypoglycemia. The risk of a completely normal glycemic profile in a type I diabetic can be likened to that of a normal speed pattern in an automobile with defective brakes. It is hoped that by raising the glycemic target levels to slightly above normal, by applying more stringent criteria for selection of patients, and through more intensive training and surveillance of the patients selected, the risks of this therapeutic approach may be maintained at a negligible level while its long-term prophylactic value is assessed. Those of us who favor the application of meticulous control would find it both tragic and ironic if these potentially preventable untoward events were to discredit this promising therapeutic program.

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