

Virtually Continuous Euglycemia for 5 Yr in a Labile Juvenile-onset Diabetic Patient Under Noninvasive Closed-Loop Control

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The author, diabetic for 33 yr, has used a novel technique for maintaining blood glucose (BG) in the 60—120 mg/dl range and HhA_{1c} in the 3.95—6.4% range, thereby lowering serum triglycerides from 200+ to 29 mg/dl, cholesterol from 250+ to 130 mg/dl, and insulin dosage from 80 to 25 U/day. BG is patient-monitored six times a day with Dextrostix and Ames Eyetone reflectance colorimeter, modified for battery operation. BG levels over 115 mg/dl are corrected with Regular insulin, 0.5 U for every 15 mg/dl elevation above 100 mg/dl. BG levels below 85 are treated with one glucose tablet (Dextrosol) for every 15 mg/dl below 100 mg/dl. Usual preprandial split insulin doses are: 5 U Regular (R) +5 U Ultralente (UL) about 50 mm prebreakfast, SR about 50 mm prelunch, and SR + 5UL about 50 mm presupper. High protein diet limits carbohydrate to one bread exchange per meal, no simple sugars, no fruits. Caloric distribution is approximately 15% CHO, ~45% PRO, ~40% fat. This diet eliminates postprandial BG elevation without the large doses of R that might cause severe hypoglycemia when meals are slightly delayed. Snacks are contraindicated unless covered by additional R. Meals may be skipped or taken at any time provided R is withheld or timed as appropriate. Psychological and physiologic improvements experienced by the author and other patients are described. The method is recommended to investigators as a means for testing long-term effects of euglycemia on sequelae of insulin-dependent DM in humans.

I am 45 yr of age and have had so-called "labile" juvenile-onset diabetes for 33 yr. Zero levels of serum and 24 h urinary C-peptide attest to the total absence of any endogenous insulin that might facilitate control of my blood glucose levels. For many years, I experienced, daily, the extreme swings of blood glucose (BG) that are characteristic of juvenile-onset diabetes. Nevertheless, for the past 5 yr my BG levels throughout the day have been essentially normal, with a typical daily range of 60—120 mg/dl (as measured in capillary whole blood). This degree of BG control has brought about the glycosylated hemoglobin values and the improvements in serum lipids shown in Table 1.

During these recent years, I have benefited from the reversals of a number of minor diabetic complications, including mild osteoporosis, chronic formation of renal and submaxillary calcium oxalate calculi, bilateral xanthomas, and chronic acne. Measurements of bilateral conduction velocities of median, ulnar, peroneal, and posterior tibial nerves are currently within the normal range. On a more subjective scale, I no longer suffer from chronic fatigue and usually get by with 5 h of sleep nightly, instead of the 8 h formerly required. I feel and appear stronger and healthier than I did 6 yr ago and no longer suffer from chronic hunger. The psychodynamic changes I have experienced are in line with those described by Dupuis,⁷ and the frequency of clinically symptomatic hypoglycemia has dropped from an average of two episodes daily to under 12 per year.

REGIME:

The regimen I have followed has been subsequently applied, with variations, by several investigators¹³ to a number of other patients with similar results. It is based on the following elements: (1) The use of insulin in physiologic (i.e., low) doses, that approximate normal pancreatic B cell output. (2) Closed-loop feedback of BG data via frequent self-monitoring of BG, followed, when necessary, by calibrated doses of insulin or oral glucose to correct minor deviations from optimum range. (3) A low-carbohydrate (CHO), high-protein (PRO) diet that minimizes glucose loading so that nonphysiologic doses of insulin are not required.

lipotrophy eventually disappeared. I find that injection sites appear to heal completely within 24 h vs. the 3–4 wk experienced previously for single doses of 80 U. This is probably due to the small volumes injected in any one dose.

TABLE 1
Improved glycosylated hemoglobin and serum lipid levels brought about by blood glucose control

	Before new regimen	Recent value—Sept. 1979	Lowest value during new regimen	Approximate normal range
HhA _{1c} , (%)	Unknown	4.0	3.95	4.4–6.0
HDL (mg/dl)	Unknown	86	—	Normal: 30–55 Low risk: >55
Triglycerides (mg/dl)	200+	69	29	50–160
Total cholesterol (mg/dl)	250+	187	130	120–300
Urine protein (mg/24 h)	Unknown	45	35	25–70

HDL, high-density lipoprotein.

Insulin regimen. My total daily insulin dose of 25 U or 0.4 U/kg body weight is split, via three injections, in a manner that provides a constant basal blood level on which are superimposed three peak blood levels to cover three meals. Forty percent of the daily dosage, or 10 U, taken as Ultralente insulin (UL) is split into two basal doses while 15 U of Regular insulin (R) are divided into three equal preprandial doses. The net regimen of subcutaneous injection is according to the following schedule: 50 mm prebreakfast, 5 U R + 5 U UL mixed in one syringe; 50 mm prelunch, 5 U R; and 50 mm presupper, 5 U R + 5 U UL mixed in one syringe.

The 50-mm interval between insulin administration and meal time permits a protective level of R to reach the bloodstream during the meal. The approximate time interval appears to vary considerably from one patient to another, being as brief as 30 mm in patients producing significant quantities of endogenous insulin and as lengthy as 90 mm in some of the patients with zero C-peptide levels. A suitable delay between administration of R and the start of a meal is essential to the prevention of postprandial hyperglycemia. If the preprandial dose of R is suitably small, the hazard of hypoglycemia due to moderate unanticipated additional delays can usually be avoided.

Minimizing the doses of long-acting insulin appears to smooth out the usual peaks, to provide a very constant basal blood level. Minimizing the total daily insulin dosage has the added advantages of reducing the trauma of injection as well as the likelihood of lipotrophy or lipohypertrophy. In my case, total daily insulin was reduced from 80 U in one injection to a total of 25 U in split doses, and long-standing insulin

Feedback control of BG. Any combination of fixed basal and preprandial insulin doses is certainly not going to compensate for the minor fluctuations in BG that are brought about by the variables of daily living. Changes in physical activity, estimation of food portions, site of injection, (possibly) emotions, etc., all can affect the glycemic state. For those diabetic persons without endogenous insulin supply, the affects of certain of these daily changes are exaggerated, because even slightly elevated BG levels tend to foster further upward drift in BG due to the increasing peripheral and hepatic resistance to insulin, as BG rises. It is therefore necessary to frequently check BG to take appropriate corrective action. The BG measurement schedule that I use is simply:

- immediately before each preprandial insulin dose.
- 2–3 h postprandially.
- On retiring for the night.
- At the first suspicion of possible hypoglycemia.
- Before, after, and midway through planned physical exercise periods.

I, therefore, may perform five to seven measurements on a typical day and have, over the past 8 yr, made more than 15,000 BG determinations. It is interesting to observe, in a recent report from Vienna by Irsigler and Kritiz,⁴ that patients using their portable insulin dosage apparatus (PIDRA) similarly performed four to seven BG measurements daily. I use Dextrostix, together with an Ames Eyetone reflectance colorimeter, that has been modified for battery operation. .1.

I aim for a continuous target BG level of 100 mg/dl and take positive remedial action if BG reaches the upper or lower limit of the range 85–115 mg/dl. To facilitate BG correction, I have calibrated both Regular insulin and glucose candies in standard BG units. For example, 0.5 U of R lowers my BG by 15 mg/dl, and one Dextrosol candy (CPC, Ltd., Esher, Surrey, England) raises it by the same amount. The calibration for R is valid, for me, up to BG levels of about 250 mg/dl. Beyond that point it appears to lose effectiveness as resistance to insulin increases. It is interesting to note that the above insulin calibration, which equals 0.5 mg/dl per unit R per kilogram of body weight, appears to be valid for many nonobese adult patients, provided they are not producing endogenous insulin. Nonobese patients, with some B cell activity, will show varying degrees of exaggerated response to additional doses of R

* Dextrostix and Eyetone are products of the Ames Company, Elkart, Indiana 46514. The battery modification can be achieved by replacing the power cord with a miniature phone jack that mounts on the rear of the Eyetone. Two 9-V rechargeable batteries are wired, via snap connectors, in series to a miniature phone plug that can be inserted in the jack during operation.

For such patients and for the obese or growing patient. the effects can be gauged experimentally.

Thus, it can be a simple matter for me, or other diabetic

patients, to bring a deviant BG back to the target level of 100 mg/dl via regulation with R or counterregulation with glucose candies and the like.

The high-protein, low-carbohydrate diet. Consider the fact that one large apple or two small scoops of ice cream or one large baked potato will each rapidly raise my BG to at least 250 mg/dl, from my target value of 100 mg/dl. To prevent this elevation I might administer at least S U of R in a precisely timed fashion and hope that the rate of entry of insulin to the bloodstream will match the rate of increase in BG. Although this may be possible with a slow intravenous insulin infusion,⁴ I cannot achieve it by subcutaneous injection.

The same problem arises if I load a meal with foods containing complex CHO. The combined effects of several bread exchanges will tend to raise BG too rapidly and too far for comfortable control. The dose of R required to cover a high CHO meal becomes so great and its activity peak so pronounced that the effects become nearly impossible to control. A slight additional delay in mealtime results in severe hypoglycemia. If a high CHO meal is eaten a little too early, the resultant BG elevation puts me into the insulin-resistant range and the prior dose of R becomes inadequate. My diabetes does, indeed, become very labile—if I load my meals with CHO as, for example, prescribed in the current ADA position statement (fat: 20–38%; PRO: 12–20%; CHO: 50–60%). Finding no other solutions to the problems generated by CHO loading, a new diet evolved that encompasses the following features: (1) Total elimination of simple sugars and fruits, except during strenuous exercise or for elevation of low BG levels. (2) Low CHO—approximately 15% of total calories and limited to one bread exchange per meal—usually taken as vegetables or salad dressing or associated with high-protein packaged foods, (3) High PRO—at least 45% of total calories with concentration on lean meats, fish, and products with low fat content. A typical meal contains six lean meat exchanges. (4) Restriction of fat to no more and preferably less than 40% of total diet, much of it derived from high-protein products and polyunsaturated whenever possible. (5) Approximately equal distribution of PRO calories and CHO calories among each of the three meals.

The protein portion of the diet serves as a slow source of CHO⁶ and is apparently adequate in this respect, since I have experienced no ketosis since starting this regimen more than 5 yr ago. The glucose produced from protein by gluconeogenesis appears to be adequately covered by the small preprandial dose of R.

Snacks are unnecessary in this regimen. They are permitted if restricted to PRO and fat (e.g., cheese), provided that the PRO portion is covered by a small dose of R, which may be administered immediately before or after a snack. The

time required for digestion of the PRO corresponds, approximately, to the absorption period of subcutaneously injected R.

Other labile patients seem to fare similarly well on this diet. Patients, producing endogenous insulin, usually can tolerate more CHO and can frequently consume small snacks without requiring extra insulin.

While patients readily adapt to the routine of multiple daily BG measurement and injections, some difficulty is encountered in securing adherence to a diet so restricted in CHO. The feedback of BG data does, however, offer a major impediment to dietary indiscretion. Patients rapidly learn the magnitude of the deleterious effects of various goodies upon BG and become loath to stray too far from their target BG range. They are, by the way, grateful that meals need not follow a rigorous timetable and can even be skipped, provided, of course, that the appropriate dose of R is similarly shifted in time or skipped. This is possible because the long-acting insulin is administered in such small amounts that there are no meal time peaks in blood levels of insulin.

SUGGESTIONS TO CLINICAL INVESTIGATORS

For any investigators who may be interested in pursuing a regimen such as the one described, I have a few suggestions based upon my own teaching experiences: (1) Train patients in small groups of three to five people rather than alone or in larger groups. The group psychodynamics will reinforce compliance and enthusiasm. Larger groups move too slowly and get bogged down by frequent questions and comments. (2) Where possible, use the assistance of patients, already trained, to serve as role models. The personal experience of a patient can, perhaps, be more convincing at the outset than can the observations of a professional clinician. (3) Be available for daily telephone contact with patients newly introduced to such a regimen. (4) Give the patient, initially, adequate time to perfect his technique of BG measurement before introducing any major modifications of insulin and diet. (5) Do not attempt to make gradual changes from an old insulin diet regimen to the new one. This can lead to a prolonged transition period where nothing seems to be working properly. It is very frustrating to patients and can be hazardous in terms of an increased potential for hypoglycemia. Any major changes from an old regimen should, therefore, be instituted promptly, after the patient has perfected a technique of BG measurement. (6) Use measurement of HbA1c or of total hemoglobin glycosylation⁷ as a rough gauge of the accuracy of patients' log books.

CONCLUSION

The customary modes of treatment for labile insulin-dependent diabetes, with urine testing and one or two daily injections of intermediate- or long-acting insulins, can be likened to the classic experiment performed in the Psychology I laboratory. Rodents are taught that depression of the correct button will produce food and that pressing the wrong button will bring about an electric shock. When the operating rules are suddenly randomized, the animals become "neurotic." Insulin-dependent patients, usually, are taught an elaborate set of "logical" rules, which, if followed, will supposedly preserve their physiologic well-being. They are rarely told that the usual rules just do not work. As a result we see anger, self-blame, and similar

responses to the wild, random swings in BO that are frequently experienced. Despair, anxiety, chronic depression, oral fixations, dependency conflicts, impaired self-image, and so on are hut some of the neurotic traits that have been attributed to these patients. 1,8—10

I, of course, have experienced many of these feelings and relate them, principally, to the frequent extremes of glycemic state over which I had virtually no control, as well as to the ever present threats of potential blindness, renal disease, impotence, and other typical sequellae of long-term diabetes. The relief, brought about by the ability to effectively predict and control glycemia and probably to prevent sequellae, is something that I will never give up. The minor inconveniences of three or four daily insulin injections and five to seven daily finger-pricks are minute in comparison to the chronic tension under which I lived for many years.

My feelings—and those of other patients using the above regimen—were, perhaps, implied in the aforementioned report of Irsigler and Kritz⁴ “. . . once the patients had experienced the facility with which good control could be achieved. . . , they found it hard to accept termination. . . .” Fortunately, for some of us who, possibly with third-party aid, can afford the materials now available for the maintenance of a physiologic glyvemic state, termination is out of the question.

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