TACTICS FOR TYPE I DIABETES

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This article discusses the evolution of therapy for type I diabetes and considers how physicians should be thinking about the disease in the late 1990s. The biases herein are that management strategy has evolved such that contemporary practice should routinely entail a system of "flexible intensive therapy" directed at meticulous glycemic control; that to accomplish this requires a skilled management team including an educated motivated patient and family working in a negotiated therapeutic alliance; and that a further goal should be the development of effective approaches to interdict the pathogenetic process such that disease prevention is possible.

CONTEMPORARY MANAGEMENT OF TYPE I DIABETES

Over the past two decades, the overall therapeutic strategy for managing type I diabetes has changed dramatically. Major advances have been made in the way insulin therapy is used in clinical practice. Much of the progress is a consequence of three factors: (1) the introduction of self-monitoring of blood glucose (SMBG) into routine practice; (2) the change in philosophy of diabetes management such that patient self-management and flexibility in lifestyle now drive contemporary treatment approaches; and (3) the demonstration that meticulous glycemic control reduces the risk of chronic complications.

In the United States in the late 1960s, the vast majority of patients with type I diabetes took only one daily injection of insulin, usually NPH or Lente. Patients were prescribed meal plans (or "diabetic diets") consisting of three meals and three snacks per day and were recommended never to skip meals and to keep consistent meal times. The proportion of calories derived from carbohydrates, proteins, and fats was defined rather arbitrarily (40%, 20%, and 40%). Monitoring of diabetes was carried out by messy urine testing, and debate
concerned whether this should be a first void or a double void. Physicians caring for diabetic patients had no easy way to assess overall chronic glycemic control.

By the early 1970s, treatment regimens began to involve split or mixed insulin programs or both. Insulin was divided into two doses with mixing of regular or Semilente insulin with NPH or Lente insulin. Some decisions were based on the supposed pattern of response to intermediate-acting insulin.16 Rigid diets and urine glucose monitoring still prevailed. With time, split-and-mixed insulin become a prominent treatment program based on the notion that there was one insulin component for each time period of the day—morning, afternoon, evening, and overnight.32

In the mid-to-late 1970s, SMBG was introduced into clinical practice.2,48 Although met with considerable skepticism by much of the diabetes treatment establishment, the introduction of SMBG permitted glycemic targets to be defined and occasionally achieved. Around the same time, glycosylated hemoglobin (HbA1c) determinations were introduced as a means of assessing chronic glycemic control.17,36

In the late 1970s, portable pumps became available to provide continuous subcutaneous insulin infusion (CSII).37,47 With the use of CSII, excellent glucose control could be achieved as assessed by HbA1c. Of even more significance, the introduction of CSII emphasized the importance of distinguishing basal from prandial insulinemia. CSII permitted greater flexibility in meal timing, meal size, meal composition, and the ability to skip meals.18

The next development in the early 1980s was the emergence of intensive insulin therapy or, more accurately, intensive therapy of type I diabetes as a therapeutic strategy.36,45 This management approach increasingly was used in diabetes centers throughout the world and included several important therapeutic elements (Table 1). In general, intensive therapy involves multiple insulin components for different time periods of the day, balancing food intake with activity and insulin dosage, frequent monitoring of therapy, and variable (but defined) treatment goals which often are based on the achievement of near-normal glycemia.

By the late 1980s and early 1990s, flexible insulin therapy (also called "basal-bolus insulin therapy" or "functional insulin therapy") began to supplant intensive insulin therapy.26,29,31,52 Flexible insulin therapy specifically emphasizes the need for preprandial insulin before each meal, separate from basal insulin, and allows more liberal food choices (particularly in terms of size, timing, and potential omission of meals) while still balancing food intake with activity and insulin dosage and including even more frequent monitoring of therapy to promote a more normal lifestyle. Use of "carbohydrate counting" rather than "exchange lists" has made tailoring insulin doses to food intake easier for many patients.15

Table 1. ELEMENTS OF A SYSTEM OF INTENSIVE THERAPY FOR TYPE I DIABETES

| 1. A multiple-component insulin program |
| 2. Careful balance of food intake, activity, and insulin dosage |
| 3. Daily self-monitoring of blood glucose |
| 4. An action plan for patient adjustment of food intake and/or insulin dosage and the use of insulin supplements |
| 5. Defined target blood glucose levels (individualized) |
| 6. Frequent contact between patient and staff |
| 7. Patient education and motivation |
| 8. Psychologic support |
| 9. Assessment of glycosylated hemoglobin (HbA1c) |
In the 1990s, the results from the Diabetes Control and Complications Trial (DCCT) were published demonstrating dramatic lessening of the risk for chronic complications of diabetes when intensive therapy is used and meticulous glycemic control achieved. The results of the DCCT forever changed the philosophy of diabetes treatment, mandating that meticulous glycemic control be the therapeutic goal.

The results of the DCCT reiterated an important premise of contemporary insulin programs (both intensive and flexible), namely that patients are the key partners in day-to-day management of diabetes. They must assume the responsibilities. It is incumbent upon health professionals to ensure that patients are adequately prepared for the day-to-day challenges they must face.

"Unrestrained creativity" is needed in matching the therapeutic regimen, in particular, the insulin distribution, to the lifestyle of the patient. This becomes particularly important for patients with chaotic schedules, unpredictable varying work shifts, changing time zones, and intermittent bursts of physical activity. Maximum flexibility in insulin administration without sabotage of glycemic control is achievable only by CSII.

The DCCT accented the critical role of various diabetes team members, in particular, that of the diabetes nurse specialist and a flexible dietitian.

Attention to the overnight period is important if glycemic control is to be attained without unacceptable hypoglycemia. In the DCCT intensive therapy group, patients were asked to obtain middle-of-the-night glucose measurements on a weekly basis. More than 86% of the measurements were obtained. The findings revealed that more than half of the serious hypoglycemia occurred overnight. Thus, clinicians must be more vigilant in their assessment of the overnight period, a period during which both patients and physicians are too often "blind" to glycemic variation. Complex changes occur during the overnight period, including a sleep-related increase in insulin sensitivity and consequent proneness to hypoglycemia, a preawakening decrease in insulin sensitivity (the "dawn" phenomenon) and consequent potential of peribreakfast hyperglycemia, and a potential variability of action (peak and duration) of multiple components of exogenous insulin. Patients may fare much better overnight, by incorporating into treatment programs both appropriate assessment, currently, with intermittent blood glucose measurements but in the future with continuous glucose sensing, and appropriate insulin delivery, either by careful timing of insulin injections or, ideally, by variable basal infusion rates with CSII.

Another lesson gained by the DCCT is the importance of careful record keeping on a prospective basis and in a manner suitable for the assessment of patterns of glycemic response so that they can be used and interpreted on an ongoing basis for adjustment of the therapeutic regimen. This means that blood glucose values cannot be buried in the memory of a meter. Detailed printouts (in a plethora of useful and useless formats) are helpful only if the information is examined on a regular and continuing daily basis, such as on a computer screen.

Patients should routinely ask themselves four questions before meals to facilitate the use of blood glucose data. These four questions are as follows: (1) what is my blood glucose now? (2) what do I plan to eat now (i.e., usual size meal, large meal, or small meal; how much carbohydrate)? (3) what do I plan to do after eating (i.e., usual activity, increased activity, decreased activity)? and (4) what has happened under these circumstances previously? The answers dictate the treatment response, which might include alterations in food intake (size or content of food), activity, insulin dosage, timing of injections in relation to meals, and insulin injection site. Meticulous glycemic control can only be
achieved with frequent blood glucose measurements and actions taken based on the results.\textsuperscript{40}

Another use of blood glucose data is in the determination of patterns of response.\textsuperscript{46} For this purpose, the overall patterns of blood glucose data are examined over several days. In response, the patient can gradually tailor, model, or shape the insulin dosage to his or her usual needs. The algorithms provided to the patient for this purpose are an ongoing iterative titration process based on experience.

Several innovations have occurred in diabetes management. Some seemingly trivial advances have turned out to be very desirable. Other highly promoted advances have turned out to be useless. Examples of useful advances include insulin pens\textsuperscript{10} (which have not become popular in the United States, uniquely) and the "quick release" system for disconnecting insulin pumps from indwelling tubing during exercise, showers, swimming, or sexual intimacy. Examples of useless advances include "jet" insulin injectors and premixed insulins (useless in type I diabetes but acceptable in type II diabetes in some circumstances).

In recent years, the authorities that make such pronouncements (the American Diabetes Association and the American Dietetic Association) have asserted that sucrose and other concentrated sweets are acceptable carbohydrates for individuals with diabetes and can be substituted on a gram-for-gram basis.\textsuperscript{3, 26} Technically, that may be true, at least in limited quantities under carefully controlled conditions.\textsuperscript{6, 9} However, this advice is contrary to real-world observations made by patients and health care professionals who have observed that the use of sucrose and concentrated sweets often results in profound hyperglycemia not otherwise explainable. The author can think of no logical reason why the two previously mentioned organizations should advocate use of such carbohydrates, which too often tend to disrupt glycemic control. However, they should not be banned altogether, because occasional use, along with increased insulin, is readily accomplished.

The recent introduction of the rapid onset, short-acting insulin analogue lispro (Humalog, Eli Lilly, Indianapolis, IN)\textsuperscript{30} permits injections immediately before meals rather than the 20 to 40 minutes before meals needed for optimal administration of regular insulin.\textsuperscript{94, 34} As a consequence, lispro has been hailed by patients as making their lives easier. However, several pitfalls are also associated with the short duration of action of lispro. The prolonged tail of the action curve of regular insulin contributes to basal insulinemia between meals. Thus, some patients on basal-bolus insulin programs can take a bedtime injection of NPH or Lente insulin and preprandial regular insulin. The author’s preference has been to include a small amount of NPH or Lente insulin as a morning injection to provide basal insulinemia during the day and avoid the potential of hyperglycemia if lunch or supper are delayed and the effect of the previous dose of regular insulin has waned. With lispro insulin, the additional morning injection of NPH or Lente insulin as a morning injection to provide basal insulinemia during the day and avoid the potential of hyperglycemia if lunch or supper are delayed and the effect of the previous dose of regular insulin has waned. With lispro insulin, the additional morning injection of NPH or Lente insulin is essential to ensure adequate basal insulinemia during the day, because there is no tail effect as with regular insulin. Indeed, some patients may need a small amount of NPH or Lente insulin with the presupper injection of lispro if there will be a long interval until bedtime and bedtime hyperglycemia occurs as a consequence of the waning effect of presupper lispro.

Lispro has been shown to be an effective insulin in CSII.\textsuperscript{53} By using lispro in this manner, basal insulinemia is ensured, and prandial boluses can be given immediately prior to meal consumption. The use of lispro in CSII seems to be the most ideal way of achieving meticulous glycemic control with a totally
flexible approach. The only downside is that care must be taken to ensure that insulin delivery is not interrupted. Thus, in contrast to a 2- to 3-hour planned interruption of insulin delivery for exercise, such as water sports, interruption of only 1 hour is possible with lispro. In addition, extra vigilance is needed to ensure that dislodging of the needle or other unintended interruption does not occur, as hyperglycemia more rapidly supervenes than when regular insulin is used in CSII.

THE DIABETES MANAGEMENT TEAM

Who should care for patients with diabetes—the primary care physician or diabetes specialists? The American Diabetes Association has a detailed set of standards of care for patients with diabetes. They include glycemic targets with a goal of HbA1c of less than 7% and an action limit of 8%. If those targets are met and all of the other standards of care are followed, it could be argued that is the bottom line, and it does not matter who provides routine diabetes care for any given patient. In that scenario, a diabetes specialist is only needed for the management of patients who fail to achieve the glycemic targets, for patients in whom the other standards are not being met, or for patients who have more complicated diabetes.

However, the results of the DCCT suggest that intensive management of type 1 diabetes requires special expertise. Conventional wisdom is that such expertise is best provided by a multidisciplinary team. Such teams should include, at the very least, a physician expert in diabetes as team leader, a nurse specialist conversant with the subtleties of diabetes management, and a contemporary dietitian who can help tailor a flexible meal pattern to the chaotic lifestyles of patients.

In many countries, special training in diabetes is available, and a diabetologist emerges. In some places, this is accomplished by a portion of training in internal medicine under the direction of the hospital diabetologist. In the United States, training in diabetes is part of the subspecialty of endocrinology, diabetes, and metabolism (EDM). Only in the last few years has the term diabetes been included in the name of the subspecialty, in recognition that treatment of the disease is a quantitatively important component of the practice of endocrinologists. Yet not all EDM training programs emphasize diabetes. Indeed, some are very weak in this component of the specialty. Many endocrinologists, particularly older ones, abhor the management of diabetes and readily admit it. Perhaps this is because the nondiabetes portion of endocrinology is more contemplative and diagnostic in nature. Success is measured by determination of the proper diagnosis, with therapy thereafter being straightforward. Diabetes, on the other hand, requires a frustrating persistence with therapeutic details over a protracted period. Quite a different mind set is involved. It is therefore not surprising that many well-known diabetologists are not endocrinologists but internists who have made diabetes their hobby or who have perhaps completed a specialized year of training at an established diabetes center—a year that may or may not count as qualifiable subspecialty training.

The situation had been even worse in pediatric endocrinology. The father of that discipline in the United States, Lawson Wilkins, declared that diabetes was not in the domain of the pediatric endocrinologist by definition. Therefore, almost all of Wilkins' disciples, who for many years dominated pediatric endocrinology in the United States, rejected diabetes as outside their sphere of influence. The void was filled in many ways by nutritionists, metabolism/genetics groups, and nephrologists. Diabetes was for a long time a stepchild,
and generalists provided most of the care for children with diabetes. Although contemporary pediatric endocrinologists do accept and indeed actively seek diabetic patients as legitimately in their purview, in some communities the ghosts of the past persist.

Nominal diabetes physician specialists, adult or pediatric, are not all conversant with intensive therapy and how to implement it. The author is appalled, at times, by the lack of understanding of basic tenets displayed by well-known experts. The care of patients with diabetes by nonexperts borders on the abysmal.

Managed care organizations often make attempts by their participating physicians to obtain expert care for patients with diabetes a struggle at best and impossible at worst. Somehow, managed care organizations have lost sight of the fact that whereas primary care by undifferentiated generalists may be good for the healthy (who constitute the majority), to mandate such care for those with chronic diseases such as diabetes may be akin to signing a death warrant. Flawed studies are cited which imply that patients appear satisfied with their care and that outcomes are similar. In reality, the event rates in these studies are low, and the apparent similarities of outcomes are consequent to the generally good health of the group as a whole complicated by the lack of expertise of so-called experts. The author believes that, given a choice, most (virtually all) persons with a chronic disease would prefer to be cared for by a true expert, the best they can find. Somehow that desire needs to be built into the design of our evolving health care system. Groups of internists working together with a balance between general internists and subspecialty internists could provide primary care for most of the adult population. In so doing, we would not have to sacrifice quality of care.

We must ensure that specialists caring for patients with diabetes have the requisite knowledge, skills, and experience to do it well. The author suspects that there is a shortage of such physicians, which means we must train more of them and use their skills more efficiently. We also must figure out how to provide physicians with credentials in a way that distinguishes the true diabetes expert from the nonexpert masquerading as one.

Nurse specialists who are expert in diabetes management are even harder to identify. There are only a few readily identifiable training programs. In the United States, there is a profusion of certified diabetes educators. They do a good job of educating patients in the basic knowledge and skills required to survive with diabetes, yet most are not specialists expert in diabetes management, particularly in intensive therapy. The author believes that intensive therapy cannot be implemented on a wide scale without nurse specialists. How then do we identify the ones that exist? How do we train more? How do we develop a qualifying standard for this professional group? This must be a top priority if we are to succeed in translating the results of the DCCT into wide-scale clinical practice.

The third player on the diabetes team is the contemporary flexible dietitian. These individuals are even harder to find than specialist doctors or nurses. Some would argue that the term flexible dietitian is an oxymoron. Although dietitians are in abundance, most have been trained in the old school of diabetes management—rigid diets filled with restrictions that are doomed to failure. In contrast, dietitians must express flexibility and unrestrained creativity in helping patients learn basic principles that are adaptable to any lifestyle. Rare is the patient who by his or her own free will will eat three square meals a day, 7 days a week, always on time. Such patients may exist but are not seen in the authors' practice. The naive old-style dietitian who would tell patients to do such does more harm than good. The contemporary flexible dietitian can help make life
worth living for patients previously confined by restrictions inappropriately placed on them. Rather than making it a burden, contemporary dietitians transform intensive therapy into diabetes self-liberation.

An exercise therapist has also been suggested as a routine member of the diabetes management team. There is no question that physical activity is good for diabetes management and that, in certain age groups, an exercise stress test is desirable before embarking on increased physical activity. Yet the training programs organized by exercise therapists resemble those of fitness gyms which survive financially only because most members rarely show up. The author fails to see the routine place of these individuals on the diabetes team.

The key team member is the patient. Success in diabetes management is contingent on a motivated patient forming a satisfactory therapeutic alliance with sensitive and knowledgeable individuals who constitute the other members of the management team. The author is convinced of this by his observations over the past 21 years working primarily in a public hospital in a city inundated with refugees. Even among the uneducated and illiterate, it is possible to implement successfully intensive diabetes management. This is exemplified by the diabetes and pregnancy program under the direction of the author’s colleague, Dr. Mary Jo O’Sullivan. The peak annual delivery rate in our hospital approaches 18,000 infants. A large number of these women have diabetes, both gestational and pregestational. With her team of expert full-time nurse specialists who work diligently with patients, O’Sullivan can achieve pregnancy target blood glucose levels in 90% of the women 90% of the time, even in the uneducated and illiterate patient. Motivation for a healthy baby and the caring support team that is always available make it possible.

Educating patients and various health care providers with whom patients interact in contemporary aspects of diabetes management remains a challenge, including the attainment of meticulous diabetes control. Although this requires time, effort, feedback, and active involvement of the patient, the results can be rewarding. The attainment of better glucose control should reduce the risk for complications, leading to better more productive lives.

Psychologic support is essential to successful diabetes therapy. The patient carries a huge burden in dealing with the complexities of disease management. He or she must balance and manipulate the therapeutic triad of food, activity, and insulin, test glucose levels multiple times daily, and invade the body with insulin needles and glucose lancets. A delicate balance must be maintained between hypoglycemia, with its attendant immediate risks including seizure, coma, and even death, and hyperglycemia, with its threat of blindness, kidney failure, amputation, and heart attack. Some type of psychologic support is clearly required. The question is whether this should be provided by a psychologist, social worker, or nurse or dietitian already on the diabetes team. It usually is unwise to have a psychiatrist involved, because this is not mental illness.

**INTERRUPTING THE DISEASE PROCESS—PREVENTION OF TYPE I DIABETES**

Type I diabetes mellitus arises as a consequence of immunologically mediated pancreatic islet beta cell destruction in genetically susceptible individuals. The disease process evolves over a period of years during which a number of immune markers appear which indicate the presence of ongoing beta cell damage accompanied by a progressive decline of function. The clinical syndrome of type I diabetes becomes evident when a majority of beta cells have been destroyed and hyperglycemia supervenes. However, even at disease onset, 10%
to 20% of beta cells remain. Improvement in their function accounts for the "honeymoon" period often seen during the first year after the onset of type I diabetes. The potential rescue of residual beta cells from immune destruction was the basis for the first studies of immune intervention in human type I diabetes. The goals of intervention at disease onset were to halt the destruction of beta cells, perhaps allowing residual cells to recover function, thus modifying the severity of clinical manifestations. In fact, the first experiments demonstrated preservation of beta cell function in new-onset patients and thus served to confirm the immunologic nature of type I diabetes. Yet the clinical course of the disease was not much altered. Moreover, many immune interventions were associated with unwanted side effects. As a consequence, the focus of investigation has shifted in two critical ways. First, the strategies now being tested are ones with less severe side effects. Second, the emphasis is being placed on studies designed to delay or prevent diabetes, with the hope that intervention earlier in the course of the disease will offer a better chance of preventing beta cell destruction, both because of increased beta cell mass and potentially less aggressive immune destructive responses.

During the stage of disease evolution, prediction of individuals that will develop disease is crucial for the testing of any intervention strategy. For ease of implementation, attention has focused on first-degree relatives of patients with type I diabetes, because such relatives have a 10 to 20 fold increased empiric risk of type I diabetes (approximately 3% to 6% among first-degree relatives) in comparison with the general population (prevalence of about 0.25% to 0.3%). Nevertheless, perhaps as many as 80% to 90% of individuals with new-onset type I diabetes do not have a first-degree relative previously known to have the disease. Consequently, all of these individuals would be missed by an approach that is confined to relatives. There are two options for these nonrelatives. The first is to identify combinations of genetic and immune markers suitable for screening of the general population to identify those at risk for the disease, and the second to develop a simple prevention strategy (e.g., a vaccine) that could be used in the entire population.

Current efforts involve three basic strategies of disease prevention: nicotinamide, altered neonatal nutrition, and antigen-specific therapy with insulin.

In animal models of spontaneous and induced diabetes, nicotinamide has been shown to improve beta cell regeneration, to increase insulin synthesis, and to prevent the development of clinical diabetes. There are several potential mechanisms by which nicotinamide may be beneficial in preventing beta cell destruction: by restoring beta cell content of nicotinamide toward normal by inhibiting poly-ADP-ribose polymerase (a major route of nicotinamide metabolism); by serving as a free radical scavenger, thereby limiting DNA and beta cell damage; and by inhibiting cytokine-induced islet nitric oxide production. Two large multicenter randomized, double-masked, controlled clinical trials are evaluating the effects of nicotinamide in high-risk relatives of individuals with type I diabetes. These are the European Nicotinamide Diabetes Intervention Trial (ENDIT) and the German (Deutsch) Nicotinamide Diabetes Intervention Study (DENIS).

Neonatal nutrition is thought to have a role because in some epidemiologic and case-control studies, there is a reciprocal relationship between infant breast-feeding and the subsequent development of type I diabetes. In Finland, a small prospective study suggested that exclusive breast-feeding reduced the risk of diabetes. It has been proposed that breast-feeding may be a surrogate for the absence of consumption of cow milk proteins (CMP). Although controversial, the notion has been proposed that consumption of CMP, particularly during a
critical window of vulnerability early in life, may lead to the initiation of the immunologic attack against pancreatic islet beta cells and increase susceptibility to type I diabetes. To test this hypothesis, a multinational randomized prospective study, the Trial to Reduce Incidence of Diabetes in Genetically at Risk (TRIGR), is being planned to determine whether the frequency of type I diabetes can be reduced by preventing exposure to CMP during early life. Newborns who have first-degree relatives with type I diabetes will receive either a conventional CMP formula or a formula in which the CMP has been replaced with casein hydrolysate. The intervention will be for a 9-month period, with follow-up for 10 years.

Antigen-specific therapies are increasingly being evaluated in autoimmune diseases. Insulin, a beta cell specific antigen, has been shown to delay the development of diabetes and of insulitis in animal models of spontaneous diabetes. It is possible that insulin may be acting metabolically by resting beta cell function, thereby reducing antigen expression associated with endogenous insulin secretion, making beta cells less susceptible to immune attack. More likely, insulin is acting immunologically by immunization, tolerization, or immune modulation.

In humans, four pilot studies have investigated insulin use in high-risk relatives of individuals with type I diabetes, with encouraging preliminary results. This has led to the Diabetes Prevention Trial of Type 1 Diabetes (DPT-1), a randomized, controlled, multicenter clinical trial conducted throughout the United States. DPT-1 is designed to test whether intervention with insulin during the prodromal period of the disease can delay the appearance of overt clinical diabetes. In relatives with a projected 5-year risk of diabetes of more than 50%, the protocol tests whether parenteral insulin therapy combining yearly 4-day courses of continuous intravenous insulin with daily subcutaneous long-acting human Ultralente insulin will decrease the expected rate of development of type I diabetes. Meanwhile, simultaneously identified relatives with a 26% to 50% risk over 5 years will be offered enrollment in a randomized, placebo-controlled, double-masked, clinical trial to test whether oral recombinant human insulin (7.5 mg/day) can modify immune tolerance and thus decrease the rate of development of type I diabetes.

These studies represent the first steps in what will most likely be an iterative process of evaluating interventions that could delay or prevent the clinical onset of type I diabetes. Wide-scale investigations of vaccination programs to prevent type I diabetes are also expected. In the long run, efforts at diabetes prevention are likely to be a predominant effort. Eventually, diabetes will prove to be preventable.

References


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