Insulin Regimens and Strategies for IDDM

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The discovery of insulin in 1921 at the University of Toronto and its first administration on 11 January 1922, ushered in a new era in the treatment of IDDM (1). More than 70 years of insulin research has resulted in improved purity, an availability of human insulin, and the development of insulin analogues using recombinant DNA technology to improve its pharmacokinetics. Despite these advances, attempts at physiological insulin replacement for IDDM continue to be disappointing (2). The achievement of metabolic normalization is distinctly uncommon, particularly as it relates to glycemic regulation. It is now generally accepted that this failure to obtain glycemic normalization is primarily responsible for the long-term complications of diabetes. The hyperglycemia/complications hypothesis was supported by epidemiological evidence and studies with animal models of diabetes and ultimately led to the initiation of long-term randomized prospective intervention studies (3). The largest study of this kind was the DCCT, which was initiated in 1982 (4,5). The results of this important study were recently presented at the 53rd Annual Scientific Meeting of the American Diabetes Association (13 June 1993, Las Vegas, Nevada) and provided definitive evidence of the benefits of intensive diabetes management on the long-term complications of diabetes (21). The demonstration that the relative risk for retinopathy, nephropathy, and neuropathy could be reduced by ~50% with intensive diabetes management should end the debate as to the benefits of improved glycemic control on long-term complications. However, the DCCT also underscored the difficulties faced by both patients and health-care providers in achieving the long-term goal of normoglycemia. Although a significant reduction in HbA_{1c} was observed in intensively treated subjects, few were able to maintain normoglycemia for the duration of the study.

When the complexity of β-cell insulin secretion in physiological terms is considered, it is indeed surprising that we are able to achieve the level of metabolic regulation usually seen in IDDM with the currently available methods of insulin replacement. Insulin is secreted from the β-cell in a pulsatile fashion in response to various secretagogues (e.g., glucose and amino acids) and is released into the portal circulation. The high portal vein insulin concentrations are probably physiologically important and this route of insulin secretion also allows the liver to function as gatekeeper in relation to systemic insulin delivery. Insulin secretion is regulated by exercise, both acutely and in response to long-term training (6). As in most physiological systems, feedback control provides for rapid changes in hormone secretion in response to a changing metabolic milieu.

UNDERSTANDING THE LIMITATIONS OF SUBCUTANEOUS INSULIN ADMINISTRATION

— As with any hormone replacement, the principal goal is to achieve physiological hormone levels at the site of hormone action. Depending on physiological needs and pharmacokinetics, this goal may be relatively simple. For example, thyroid hormone replacement can be readily achieved with one daily oral ingestion of L-thyroxine. The half-life of thyroxine is long (7 days) because the hormone is bound to circulating proteins. This stable reservoir of hormone serves well the physiological requirement of a constant concentration of free thyroxine at tissue sites of action. In contrast, insulin is a hormone with a short half-life (5–7 min) and a physiological profile that requires rapid changes in concentration (by severalfold) in response to nutrient intake and other physiological stimuli like exercise.

When examining the usual route of insulin administration, namely the subcutaneous injection site, several studies have shown that numerous variables influence insulin absorption and, as a consequence, circulating insulinemia (Table 1). It is now well established that the rate of insulin absorption varies considerably depending on injection site

Table 1—*Variables affecting insulin absorption*

Site of injection
Depth of injection
Insulin species
Insulin mixtures
Insulin dose
Exercise
Local heat

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IDDM, insulin-dependent diabetes mellitus; NIDDM, non-insulin-dependent diabetes mellitus; DCCT, Diabetes Control and Complications Trial; HbA_{1c}, glycosylated hemoglobin A_{1c}; CSII, continuous subcutaneous insulin infusion; MDI, multiple daily insulin injection.

selection (7). The rate of insulin absorption decreases progressively when comparing abdomen to arm to leg. These differences can be substantial. It has been shown that ^{125}I-labeled regular insulin disappears 86% faster from the abdomen than from the leg.

If we are attempting to maintain consistency in nutrient intake in relationship to insulin dose for a specific meal, it seems evident that we maintain consistency with reference to the site of insulin injection. This is contrary to the traditional advice we give, which is to rotate injection site to avoid lipodystrophy. If the patient is willing to use the abdomen as the principal injection site, one can often rotate systematically throughout the large abdominal area and thus eliminate the factor of injection-site variability. If this is not acceptable, a consistent injection site should be used for a particular component of the insulin treatment regimen (example, prebreakfast insulin dose is always injected in the arm) to minimize the effect of this variable. The depth of injection and the ambient temperature also can affect insulin absorption and consequent insulinemia.

The effect of exercise on subcutaneous insulin absorption has been well documented in both animal and human studies. When insulin is injected into an extremity and that limb is exercised, marked acceleration in insulin absorption can occur (8,9). The pharmacokinetics of insulin absorption also are influenced by the insulin species, the dose, and the interaction of various modified insulin preparations. Human insulin is absorbed more quickly than animal insulins, a property that can result in improved postprandial glycemic control (10). Increasing the doses of insulin results in a delayed time-to-the-peak action, and significantly extends the duration of action. Mixing regular insulin with lente insulin in the same syringe results in a delay in the absorption of the regular insulin component. This does not occur when regular insulin is mixed with NPH insulin (11). However, in controlled studies, these differences did not translate into significant differences in glycemic control because many other variables also influence glycemic regulation (12). Despite our best efforts at controlling the variables affecting insulin absorption, intrasubject variation remains considerable: peak insulin concentration still may vary by 39% and time-to-peak insulin concentration by 51% (13).

Table 2—*Intensive insulin therapy*

MDI
Intermediate-acting insulin based (NPH, Lente)
Long-acting insulin based (Ultralente)
CSII

CONVENTIONAL INSULIN THERAPY VERSUS INTENSIVE INSULIN THERAPY

Conventional insulin therapy can be described as the administration of 1 or 2 injections of insulin (usually before breakfast and dinner), coupled with blood glucose self-monitoring and the adjustment in insulin dose in response to the glycemic pattern. Diabetes education and dietary counselling focus on administering insulin, understanding insulin action, recognizing and managing hypoglycemia, adjusting treatment regimen for exercise, monitoring the effects of hyperglycemia and ketosis, managing sick days, maintaining ideal body weight, and avoiding the complications of diabetes through proper surveillance.

In contrast, intensive insulin therapy, by definition, attempts to simulate physiological insulin needs more closely. The strategy of insulin administration consists of providing independently both basal insulin and meal insulin requirement and allowing for rapid adjustment in each component. The insulin treatment regimen involves 3 or 4 daily injections or the use of an insulin pump for CSII (Table 2). The specifics of each of these approaches have been described previously in great detail and will not be repeated here (14). Rather, I will focus on general principles and recommendations.

Many modifications of MDI regimens have been proposed and generally can be classified as intermediate- or long-acting insulin based (Table 3). Insulin species is an additional variable to consider when prescribing an intensive treatment regimen. Because human Regular insulin is absorbed more rapidly than pork insulin (10), it is the preferred insulin for meal requirements. However, when considering basal insulin requirements, beef/pork Ultralente has a longer

Table 3—*Multiple daily insulin-treatment regimens*

	Breakfast	Lunch	Dinner	Bedtime
Intermediate insulin based*				
	Regular	Regular	Regular	NPH
	NPH		Regular	NPH
	Regular			
Long-acting insulin based†				
	Regular/Ultralente	Regular	Regular	
	Regular	Regular	Regular/Ultralente	
	Regular/Ultralente	Regular	Regular/Ultralente	
	Regular	Regular	Regular	Ultralente

*Lente can be substituted for NPH.

†With Ultralente-based regimens, insulin species is an important consideration. Beef/pork Ultralente has a longer duration of action and 1 injection may suffice, whereas human Ultralente is shorter acting and 2 injections may be required.

duration of action and, for most purposes, can be considered peakless when compared with human Ultralente. For patients not previously taking animal insulin, it may be more appropriate to use a twice daily dose of human Ultralente for basal replacement rather than a single dose of beef/pork Ultralente. In the context of human insulin, several reports have suggested an increased frequency of hypoglycemia unawareness with human insulin when patients are switched from beef/pork (Cryer, this issue, p. 40–47). Other investigators have failed to confirm this observation and it generally is believed that it may represent a idiosyncratic reaction in a small number of patients. The use of insulin injection devices like the insulin pen make MDI regimens more acceptable.

Independent of the particular insulin regimen being used, it is clear that self-blood glucose monitoring is fundamental to achieving success with intensive insulin therapy. An algorithm or variable insulin-dose schedule has to be developed to help determine the appropriate insulin dose for the next meal. In general terms, three important variables determine meal insulin requirements. These include the carbohydrate content of the meal, the premeal glycemic concentration, and the anticipated exercise activity after the meal. Basal insulin requirements are determined by before-breakfast glycemic levels and periodic 0300 glucose measurements to assess overnight glycemic control. To achieve success with intensive insulin therapy, the patient must develop self-management skills appropriate for this form of treatment (15).

In addition to the diabetes and dietary education goals of conventional therapy, the individual must be comfortable with using meal-to-meal insulin-dose adjustments to compensate for the inadequacies of subcutaneous insulin replacement. This form of "closed loop", insulin feedback depends on frequent self-blood glucose monitoring and maintaining a reasonably consistent diet. Indeed, it has been clearly demonstrated that self-monitoring is the most important variable in determining success, as measured by HbA_{1c} (14). Monitoring before meals and at bedtime is the minimum requirement for intensive treatment regimens and, frequently, additional testing is required (e.g., postprandially, in relationship to exercise, and at 0300).

It is important to emphasize that insulin administration is only one component of intensive diabetes management and that skills in self-management and dietary considerations often are the difference between success and failure. In this context, the effective use of the diabetes health-care team, which includes the patient, nurse educator, dietitian, physician, and other required support staff, is essential.

RISKS AND BENEFITS OF INTENSIVE INSULIN THERAPY— The most significant and well-documented risk of intensive insulin therapy is an increased frequency of severe hypoglycemia. Severe hypoglycemia, as defined by the DCCT, is "an event with symptoms consistent with hypoglycemia in which the patient required the assistance of another person and which was associated with a blood glucose level <50 mg/dl (2.8 mM) or prompt recovery after oral carbohydrate, intravenous glucose or glucagon" (16). This would include patients who experienced confusion, coma, or seizure as a result of hypoglycemia.

Recently, the DCCT Research Group reported that, over the course of the study, the incidence of severe hypoglycemia in the intensive treatment group was ~3 times that observed with standard treatment. Severe hypoglycemia was more common during sleep (55% of episodes), and it was associated with longer duration IDDM, a history of previous severe hypoglycemia, higher baseline HbA_{1c} at randomization, and lower recent HbA_{1c} (16). The changes in counterregulatory hormone physiology with longer duration diabetes and glycemic control have been studied to better understand the development of hypoglycemia unawareness (17,18). The importance of daily glycemic variations and the frequency of recurrent mild hypoglycemia in the development of hypoglycemia unawareness has been proposed in studies examining glycemic controls with CSII, compared with an intravenous insulin infusion device (19). This important clinical problem is addressed in detail in Dr. Cryer's article. Other negative aspects of intensive insulin therapy include increased cost; greater weight gain; and, in the case of CSII, increased risk of ketosis and infusion-site infection.

Apart from severe hypoglycemia, the risks of intensive diabetes management are minimal compared with the substantial benefits demonstrated by the DCCT.

CHOOSING A TREATMENT REGIMEN— For most patients with IDDM, an intensive diabetes treatment strategy, which includes intensive insulin therapy, should be the treatment regimen of choice. The exact regimen to be used will be determined by several factors (Table 4). For intensive treatment regimens to work, the patient must be knowledgeable, assume responsibility for self-management, and have the necessary motivation and skill to achieve the goals of this therapy. The patient must have access to and be an active member of the diabetes health-care team. The amount of ongoing support is likely to vary among individual patients. However, the goals of therapy must be realistically chosen. This will depend on the patient's general health status, social support, and financial resources. The presence of concomitant severe cardiovascular or cerebrovascular disease may make intensive therapy inappropriate because of the risks of severe hypoglycemia.

Although glycemic control is

Table 4—*Choosing an insulin treatment regimen*

Assess patients' motivation, health beliefs, and potential for self-management
What are the realistic goals of therapy?
(e.g., avoid symptoms of hyper- and hypoglycemia or striving for normoglycemia)
What is the general health status?
(e.g., coronary artery disease, cardiovascular disease, etc.)
Consider social support and financial implications

clearly an important variable in determining whether long-term complications occur, other strategies for the prevention and management of complications are equally important (20). The importance of implementing systematic methods for complication surveillance as part of ongoing care cannot be overstated. Early recognition of the development of complications ensures appropriate, timely intervention. Diabetic retinopathy can be effectively managed by retinal photocoagulation. Aggressive blood pressure control retards the progression to end-stage renal failure, and proper foot care in those with peripheral neuropathy prevents ulcer formation and amputation. In addition, an alternate approach to complication prevention is being pursued by several groups. The use of pharmacological agents that interrupt the pathophysiological pathways thought to be responsible for the long-term microvascular complications is indeed a promising approach for complication prevention in the 1990s. Ongoing studies currently are examining the effect of aldose-reductase inhibitors on retinopathy, neuropathy, and nephropathy, both in IDDM and NIDDM. Another pharmacological approach to complication prevention involves the use of inhibitors of advanced glycation end-product formation.

To summarize, our current insulin treatment strategies do not provide physiological insulin replacement. The now demonstrated clear benefit of striving for normoglycemia in relationship to complication prevention should provide a powerful stimulus for technological advances (e.g., glucose sensors, insulin analogs, implantable pumps, etc.), with the ultimate goal being the achievement of long-term sustained normoglycemia.

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