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### GUEST EDITORIAL

#### WE'VE COME A LONG WAY: THE 35-YEAR JOURNEY TOWARD IMPROVED TREATMENT OF CHILDREN WITH TYPE 1 DIABETES

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I started my training in pediatric endocrinology in 1975, in an era I now like to classify as “the bad old days of type 1 diabetes treatment.” At that time, it was not unusual for youth with “juvenile diabetes” to be treated with one or maybe two daily injections of NPH insulin. The insulin preparations were extracted from beef or pork pancreases and were not highly purified; this contributed to the frequent occurrence of lipoatrophy. Even more dreadful was the fact that there was really no good way to monitor a patient’s glucose control, because blood glucose meters had not yet been introduced and hemoglobin A1C assays had not yet been developed. Nevertheless, most of us participated in the charade that we were really learning something useful by having our patients monitor their urinary glucose concentrations. I can even remember debates as to whether the 2-drop Clinitest method was better than the 5-drop approach for measuring urinary glucose, and I still shudder when I think of what it was like to try to treat a 2-year-old without blood testing.

In 1977, the National Institutes of Health published a Request for Applications for centers to participate in a study like the Diabetes Control and Complications Trial (DCCT), but the project was abandoned because there were few, if any, takers. Things began to

change in a rush, though, between 1979 and 1981:

- Publications appeared touting the usefulness of the Ames Reflectance Meter as a method for patients to measure their blood glucose levels at home
- The proportion of “fast” hemoglobin obtained from column chromatography methods, which my friends in hematology used to throw away, was found to correlate with average blood glucose levels over the previous several months
- The first insulin pump studies were conducted at Yale and Guy’s Hospital, London; this approach to insulin replacement was termed continuous subcutaneous insulin infusion (CSII) by John Pickup and Harry Keen
- Successes with CSII motivated other clinicians to develop more physiologic, multiple daily injection (MDI) insulin regimens

These advances set the stage for the DCCT, which in 1993 conclusively demonstrated that intensive treatment

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of patients with type 1 diabetes mellitus (T1DM), compared with conventional treatment, reduced the risk of development and slowed the progression of early diabetic retinopathy, as well as other complications. Of great practical importance for later studies of new drugs and devices, the DCCT established the ability to lower A1C as an effective surrogate outcome biomarker.

The dark side of the intensive treatment story is that it quickly became apparent that the treatment itself was adversely affecting the ability of patients with T1DM to recognize and respond to falling blood glucose levels. It was known already that these patients routinely lost the ability to mount a plasma glucagon response to hypoglycemia, but the degree of impaired catecholamine responsiveness observed in the DCCT was unexpected. Since the 1980s, the pathophysiologic mechanisms that contribute to the risk of severe hypoglycemia in T1DM had been under intense study. Consequently, the report that the rates of severe hypogly-

cemia were increased in intensively treated patients in the DCCT was not unexpected; however, the magnitude of the problem was surprising:

- 3-fold higher rates of severe hypoglycemic events, versus controls, in adults and youth
- 54 events of severe hypoglycemia/100 patient-years in intensively treated adults
- 87 events of severe hypoglycemia/100 patient-years in intensively treated adolescents (even though A1C levels were higher in intensively treated adolescents [8.1%] than adults [7.1%])
- Severe hypoglycemia rates were inversely and almost exponentially related to A1C levels

It has been 17 years since the end of the DCCT, and clinicians who care for children and adolescents with T1DM now have drugs and devices that enable a much larger proportion of patients to achieve and maintain target A1C levels more safely than could have been imagined back in the 1970s. As discussed by Drs. Mehta and Wolfsdorf in this issue, the introduction of rapid-acting and long-acting insulin analogs was an important first step. Compared with regular insulin, the sharper peaks and shorter duration of action of these analogs have been particularly beneficial to adolescents who require large pre-meal bolus doses to overcome the peripheral insulin resistance of puberty. Compared to NPH and lente insulins, the flat time-action profile and prolonged duration of action of long-acting insulin analogs have several advantages for basal insulin replacement, including a reduced risk of nocturnal hypoglycemia.

In addition, over the past 10 years it has been very gratifying to observe the more widespread use of insulin pumps in pediatric diabetes practice; this has transformed the care of youth with T1DM. Using the bolus history function, we can actually determine whether teenagers are taking their pre-meal bolus doses. Recent studies have shown that, with these advances alone, intensively treated youth with T1DM can achieve A1C levels <8.0%

with rates of severe hypoglycemia reduced by ≥67% compared with intensively treated adolescents in the DCCT (click on the PubMed ID number to read more: [PMID 14769830](https://pubmed.ncbi.nlm.nih.gov/14769830/)).

The treatment of youth with T1DM is fraught with multiple challenges across all stages of development except during the “honeymoon,” or partial remission, phase of the disease; this generally occurs within 2 to 6 months of diagnosis. The DCCT first demonstrated that intensively treated T1DM patients with residual  $\beta$ -cell function had better metabolic control, required lower daily insulin doses, and experienced fewer hypoglycemic events than intensively treated patients with an absent C-peptide response to a mixed meal feeding. These observations fueled interest in therapeutic approaches aimed at preserving  $\beta$ -cell function. Drs. Haller and Schatz discuss these and other burgeoning areas of research in their article in this issue.

The development of real-time continuous glucose monitoring (RT-CGM) systems has the potential to be the game-changing event of the current era, but to date, use of these systems in pediatric patients on CSII or MDI regimens has shown mixed results. In the recent Juvenile Diabetes Research Foundation CGM trial, youth aged 8 to 18 years with T1DM and A1C levels ≥7.0% fared no better with RT-CGM than control group patients randomized to receive only blood glucose monitoring. While pediatric patients who wore the sensor 6 to 7 days a week achieved a –0.8% reduction in A1C levels, <25% of pediatric patients were able to use RT-CGM that frequently over the 12 months of the study. If a larger proportion of youth with T1DM are to benefit from RT-CGM, smaller, less intrusive, more accurate, and easier to use devices will likely be needed.

It should be recognized that the increased use of insulin pumps and the introduction of CGM systems have increased the burden of therapy for patients, families, and clinical teams. Moreover, no T1DM insulin replacement regimen will be perfect until feedback

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and control of insulin delivery is available on a minute-to-minute basis. By combining external insulin pumps and glucose sensors, a number of centers and research teams have already taken the first steps toward development of an artificial pancreas. The combination of these two technologies offers the unique prospect of providing a means to optimize diabetes control, while simultaneously reducing the burden of care. A mechanical solution to the problems of insulin replacement would represent the culmination of a long journey and provide a bridge to the final cure of T1DM through islet cell transplantation or  $\beta$ -cell regeneration.

I have always found diabetes a very humbling condition with which to work. Just when you think you have an answer to a problem, new and even more challenging questions emerge. As outlined above, we have made great progress toward more effective T1DM management. Unfortunately, just as we

are on the verge of greater therapeutic breakthroughs, we are confronted with the new challenge of a growing type 2 diabetes mellitus (T2DM) incidence in obese children and adolescents. The scope and under-lying pathophysiology of T2DM in youth are well described in this issue in an article by Drs. Burns and Arslanian. It is noteworthy that these authors make no mention of treatment of T2DM in youth because, frankly, we haven't figured out the best approaches to manage this "new" type of diabetes in pediatric patients—in this way, we are now at the starting point again, learning how to manage this new manifestation of diabetes.

*Dr. Tamborlane has no commercial relationships to disclose related to the content of this article.*

### Suggested Reading

DCCT/EDIC Research Group. Beneficial effects of intensive therapy of diabetes during adolescence: outcomes after the conclusion of

the Diabetes Control and Complications Trial. *J Pediatr.* 2001;139:804-812.

Diabetes Research in Children Network (DirecNet) Study Group. Blunted counter-regulatory hormone responses to hypoglycemia in young children and adolescents with well-controlled type 1 diabetes. *Diabetes Care.* 2009;32:1954-1959.

Doyle EA, Weinzimer SA, Steffen AT, et al. A randomized, prospective trial comparing the efficacy of continuous subcutaneous insulin infusion with multiple daily injections using insulin glargine. *Diabetes Care.* 2004;27:1554-1558.

Swan KL, Dziura JD, Steil GM, et al. Effect of age of infusion site and type of rapid-acting analog on pharmacodynamic parameters of insulin boluses in youth with type 1 diabetes receiving insulin pump therapy. *Diabetes Care.* 2009;32:240-244.

TODAY Study Group. Treatment Options for type 2 Diabetes in Adolescents and Youth: a study of the comparative efficacy of metformin alone or in combination with rosiglitazone or lifestyle intervention in adolescents with type 2 diabetes. *Pediatr Diabetes.* 2007;8:74-87.

Weinzimer SA, Steil GM, Swan KL, et al. Fully automated closed-loop insulin delivery versus semiautomated hybrid control in pediatric patients with type 1 diabetes using an artificial pancreas. *Diabetes Care.* 2008;31:934-939.

## PRACTICE POINTERS

### INSULIN THERAPY IN PEDIATRIC TYPE 1 DIABETES

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The Diabetes Control and Complications Trial demonstrated in 1993 that a system of intensive diabetes management aimed at achieving near-normal glycemic control dramatically reduced the risk of microvascular complications and favorably affected the risk of macrovascular complications. Intensive diabetes management includes an insulin regimen that attempts to mimic physiologic insulin replacement (either

multiple daily injections or insulin pump), combined with medical nutrition therapy and frequent self-monitoring of blood glucose (SMBG). This article reviews current approaches to insulin therapy in pediatric type 1 diabetes mellitus (T1DM).

### Physiologic Basis for Insulin Replacement

Endogenous insulin release has two principal components. *Basal* insulin secretion suppresses lipolysis and balances hepatic glucose production with glucose utilization, while *prandial*, or *meal*, insulin release inhibits hepatic glucose production and stimulates glucose uptake after eating. Our ability to simulate normal insulin production via subcutaneous administration is limited by our inability to easily reproduce biphasic prandial insulin release and the need to deliver exogenous insulin into the systemic circulation as opposed to the portal system.

### Insulin Analogs

Pharmacologic profiles of available insulins are summarized in Table 1. Over the past 15 years, insulin analogs have been developed as alternatives to regular (soluble) and NPH insulin;

these formulations have pharmacodynamic profiles that more closely mimic either prandial or basal insulin profiles. Despite their drawbacks, regular and NPH insulin are still commonly used in pediatric diabetes. Regular insulin is short acting and imparts a substantial basal component. NPH is intermediate acting and provides a basal component; it also has a broad peak action that imparts substantial prandial coverage.

Compared with regular insulin, rapid-acting analogs (lispro, aspart, and glulisine) have a faster onset and shorter duration of action. To limit postprandial glucose excursions, rapid-acting analogs should be administered approximately 10 to 15 minutes before meals. This is a major practical advantage compared with regular insulin, which needs to be administered at least 30 minutes before a meal. In special circumstances, for example, in very young children, during sick-day management, or when food intake is unpredictable, rapid-acting analogs may be administered after eating.

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NPH insulin is a suspension-based formulation with inconsistent absorption and action; this results in variable pharmacodynamic effects. In contrast, long-acting insulin analogs (glargine and detemir) are relatively peakless, have significantly less dose-to-dose variability, and demonstrate more consistent action profiles. Long-acting analogs can often be administered once daily to achieve 24-hour basal coverage; insulin detemir, however, may require two daily injections to provide stable 24-hour basal coverage. Long-acting preparations should be administered at approximately the same time of the day ( $\pm 1$  hour) and should not be mixed with prandial insulins.

### Insulin Regimens

Intensive injection-based regimens are classified as either flexible (basal-bolus) or modified fixed dose (sliding scale). In clinical practice, regimens can be modified to accommodate the patient's lifestyle, personal preferences, and other factors (eg, insulin administration at school).

Flexible insulin regimens separate basal and prandial insulin coverage and are delivered using multiple daily injections (MDIs) or an insulin pump. Basal coverage is provided via either a long-acting analog, for injection-based therapy, or continuous infusion of rapid-acting insulin (using fixed or variable basal rates) with insulin pump therapy. Rapid-acting insulin analog doses are calculated using an insulin-to-carbohydrate ratio, based on the anticipated amount of carbohydrate in the meal or snack, as well as the current blood glucose (BG) level (using an insulin sensitivity or correction factor); additional adjustments can be made for recent or planned exercise.

A modified fixed-dose insulin regimen requires a rapid-acting analog and NPH insulin before breakfast, a second dose of rapid-acting analog before dinner, and NPH or a long-acting analog at bedtime. Alternatively, the long-acting insulin may be given with dinner. The rapid-acting analog provides prandial coverage for breakfast and dinner and is adjusted using a

**Table 1. Pharmacodynamic profiles of available insulins and insulin preparations**

	Onset	Peak action	Effective duration
<b>Rapid acting</b>			
Insulin lispro (analog)*	5-15 min	30-90 min	3-5 h
Insulin aspart (analog)*	5-15 min	30-90 min	3-5 h
Insulin glulisine (analog)	5-15 min	30-90 min	3-5 h
<b>Short acting</b>			
Regular (soluble)	30-60 min	2-3 h	5-8 h
<b>Intermediate acting</b>			
NPH (isophane)	2-4 h	4-10 h	10-16 h
<b>Long acting</b>			
Insulin glargine (analog)	2-4 h	Peakless	20-24 h
Insulin detemir (analog)	2-4 h	6-14 h	16-20 h
<b>Combinations</b>			
70% NPH, 30% regular	30-60 min	Dual	10-16 h
70% NPA, 30% aspart	5-15 min	Dual	10-16 h
75% NPL, 25% lispro	5-15 min	Dual	10-16 h
50% NPH, 50% regular	30-60 min	Dual	10-16 h

Per manufacturers' data; \*other data indicate equivalent pharmacodynamic effect (from Plank J, et al. *Diabetes Care*. 2002;25:2053-2057)

Adapted from Wolfsdorf J, ed. *Intensive Diabetes Management*. 4th ed. Alexandria, VA: American Diabetes Association; 2009 and Dewitt, DE. *JAMA*. 2003;289:2254-2264.

sliding scale (supplemental or correction insulin) according to the patient's preprandial BG level. In a modified fixed-dose regimen, the peak action of the morning dose of NPH may obviate the need for an insulin injection before lunch; however, success with this regimen requires that meals and snacks are consistently timed and are of fixed quantity.

**More than 90% of individuals who initiate insulin pump therapy do not revert to injection-based regimens.**

For a limited period after the diagnosis of T1DM, patients with persistent endogenous insulin production (ie, those in partial or complete remission) can maintain tight glycemic control using once- or twice-daily insulin regimens. In general, however, use of such regimens, including use of premixed (combination) insulins, should be reserved for patients unable or unwilling to implement intensive insulin therapy.

### Insulin Pump Therapy

The use of continuous subcutaneous insulin infusion (CSII), or insulin pump

therapy, has increased dramatically since its initial introduction in the 1970s. Current insulin pumps incorporate numerous features that facilitate various insulin dose calculations and delivery patterns. The reader is referred to the review of insulin pump therapy published in the September 2008 issue of *Current Diabetes Practice* (Volume 7, Issue 2).

Increased experience with insulin pump use and improved pump designs have significantly reduced the risk of major adverse events; however, the risk of diabetic ketoacidosis (DKA) remains marginally higher with pump therapy due to the lack of a subcutaneous insulin depot. Therefore, DKA prevention strategies must be emphasized for pump users. Additionally, skin infection at the site of cannula insertion is the most frequent adverse event, and a common reason for discontinuing pump use. Currently, more than 90% of individuals who initiate pump therapy do not revert to injection-based regimens; however females and patients who are adolescents when they start are more likely to discontinue pump therapy (click on the PubMed ID number to read more: [PMID 19566740](https://pubmed.ncbi.nlm.nih.gov/19566740/)).

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Despite efforts to optimize glycemic control, some individuals using MDI-based regimens experience recurrent hypoglycemia, unpredictable glycemic fluctuations, or persistent A1C elevations. These patients may be candidates for pump therapy. Others may simply want to avoid MDI or take advantage of the flexibility pump therapy affords. It is our practice to offer pump therapy to any individual who is informed and motivated and demonstrates the ability to adhere to the minimum diabetes self-care requirements necessary to use a pump safely. Successful implementation, however, requires the support of a diabetes team experienced in the use of pump therapy.

### Initiating Insulin Therapy

There is no standardized approach to guide insulin initiation for youth with T1DM. We describe here our approach to the child with newly diagnosed T1DM who is not in DKA (see Figure 1). The initial total daily dose (TDD) ranges from 0.25 to 1.0 U/kg; the low end of the dose range is used for prepubertal children and children who do not present with DKA. Age-specific BG targets are based on American Diabetes Association recommendations. Regardless of starting dose, frequent adjustments, guided by SMBG data, are typically required during the first weeks of therapy.

For flexible regimens, the long-acting analog dose is 50% of the TDD and should be administered at the same time each day. The rapid-acting analog covers carbohydrate intake using insulin:carbohydrate (I:CHO) ratios and corrects hyperglycemic excursions using correction factors (CFs). An initial I:CHO ratio is calculated using the formula 450/TDD; for example, if TDD=45 U, the starting I:CHO ratio is 1 U of rapid-acting analog for 10 g of carbohydrate. The initial CF is calculated using the formula 1800/TDD; therefore, for TDD=45, 1 U of rapid-acting analog will lower BG levels by 40 mg/dL. Correction doses are typically not administered more frequently than every 3 hours. The actual prandial

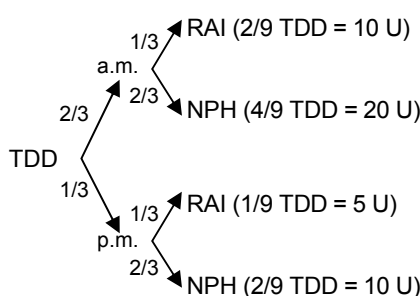
## Figure 1. Calculation of initial insulin doses

(example: starting total daily dose [TDD] = 45 units [U])

### Flexible regimen

<b>B A S A L</b>	40-60% of TDD	<b>P R A N D I A L</b>	CHO dose+correction dose (as RAI)
	• eg, 50% of 45 U ≈ 23 U		CHO dose = CHO intake/CHO ratio
	Injection: 1-2 doses of long-acting analog		• CHO ratio: 450/TDD
	Pump: Continuous infusion of RAI over 24 h		• eg, 450/45 = 1 U/10 grams
	• eg, 23 U/24 h ≈ 1 U/h		Correction dose = (BG – target BG)/CF
			• Correction factor (CF) = 1800/TDD
			• eg, 1800/45 = 1 U lowers BG 40 mg/dL

### Modified fixed dose regimen



BG	Breakfast		Lunch	Dinner	Bedtime	
	NPH	RAI	RAI	RAI	NPH	RAI
<80	20	9	0	4	10	0
80-150	20	10	0	5	10	0
151-200	20	11	0	6	10	0
201-250	20	12	2	7	10	2
251-300	20	13	3	8	10	3
301-350	20	14	4	9	10	4
351-400	20	15	5	10	10	5
>400	20	16	6	11	10	6

BG, blood glucose; CHO, carbohydrate; RAI, rapid-acting insulin; TDD, total daily dose

insulin dose is the sum of the doses required for carbohydrate coverage and hyperglycemia correction.

For modified fixed-dose regimens, a meal plan should be provided (this reinforces the need for consistent timing and quantity of carbohydrate intake). Initially, the TDD is distributed two thirds in the morning and one third in the evening. The morning and evening doses are each further divided (two-thirds NPH and one-third rapid-acting analog). The morning NPH and rapid-acting analog doses can be mixed and administered before breakfast. Typically, the evening rapid-acting analog dose is given before dinner, and the evening NPH dose is administered at bedtime. However, if there is minimal time between dinner and bedtime (eg, for very young children), the evening rapid-acting analog and NPH doses may be mixed and administered before dinner. If the child does not eat a bedtime snack, the evening NPH dose

can be substituted 1:1 with a long-acting analog. This approach also minimizes the risk of nocturnal hypoglycemia. A sliding scale of rapid-acting insulin (supplemental insulin or CF) can be used to manage preprandial BG values that exceed specified targets. Supplemental (sliding scale) insulin doses before lunch and bedtime are typically reserved for BG values >200 to 250 mg/dL and are calculated as a percentage of the TDD (5% to 10% or more, depending on the BG value).

### Conclusion

It has been suggested that flexible regimens, and pump therapy in particular, are the gold standard for intensive insulin therapy. In clinical practice, however, the use of a flexible insulin regimen does not *per se* guarantee improved glycemic control. Although these regimens have the potential to most closely simulate physiologic insulin production, the requirements for their successful implementation can limit their effectiveness for many

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children and adolescents with T1DM. Therefore, patients with T1DM should be informed about the risks and benefits of available intensive insulin regimens and encouraged to choose the regimen they are most likely to adhere to consistently and successfully.

*Dr. Mehta and Dr. Wolfsdorf have no commercial relationships to disclose related to the content of this article.*

### Suggested Reading

Danne T, Aman J, Schober E, et al. A comparison of postprandial and preprandial administration of insulin aspart in children and adolescents with type 1 diabetes. *Diabetes Care*. 2003;26:2359-2364.

Hirsch IB. Insulin analogues. *N Engl J Med*. 2005;352:174-183.

Paris CA, Imperatore G, Klingensmith G, et al. Predictors of insulin regimens and impact on outcomes in youth with type 1 diabetes: the SEARCH for Diabetes in Youth study. *J Pediatr*. 2009;155:183-189.

Silverstein J, Klingensmith G, Copeland K, et al. Care of children and adolescents with type 1 diabetes: a statement of the American Diabetes Association. *Diabetes Care*. 2005;28:186-212.

Singh SR, Ahmad F, Lal A, et al. Efficacy and safety of insulin analogues for the management of diabetes mellitus: a meta-analysis. *CMAJ*. 2009;180:385-397.

Skinner TC, Cameron FJ. Improving glycaemic control in children and adolescents: which aspects of therapy really matter? *Diabet Med*. 2010;27:369-375.

Wolfsdorf JI, ed. *Intensive Diabetes Management*. 4th ed. Alexandria, VA: American Diabetes Association; 2009.

## LITERATURE CORNER

### INVESTIGATIONAL THERAPIES FOR TYPE 1 DIABETES PREVENTION AND INTERVENTION

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Type 1 diabetes mellitus (T1DM) is an autoimmune disease process characterized by T-cell-mediated destruction of pancreatic  $\beta$ -cells. While a majority of T1DM patients are diagnosed during childhood or adolescence, at least one fourth of T1DM cases are identified in adulthood. T1DM has an estimated incidence of 10,000 to 15,000 cases per year in the U.S., and is one of the most common chronic diseases in children worldwide.

According to current models, genetic and environmental triggers both likely play a role in T1DM pathogenesis. The presence of antibodies to  $\beta$ -cell antigens (eg, insulin or glutamic acid decarboxylase 65) signals the onset of autoimmunity; however, patients are typically asymptomatic for an extended period before development of overt T1DM. With progressive T-cell-mediated  $\beta$ -cell destruction, patients lose the first-phase insulin response and develop glucose intolerance and ultimately clinical diabetes (click on the PubMed ID number to read more: [PMID 16301083](https://pubmed.ncbi.nlm.nih.gov/16301083/)).

Research is ongoing to develop new treatment modalities to prevent, halt, and/or reverse the T1DM disease process; as shown in Figure 1, these investigational approaches to T1DM interdiction can be classified based on the disease stage as primary prevention, secondary prevention, or intervention-based strategies.

The goal of primary prevention is to prevent the development of T1DM auto-antibodies in at-risk patients who have not yet developed  $\beta$ -cell autoimmunity. Historically, primary prevention research has involved the use of low-risk therapies in patients at higher risk for T1DM (eg, relatives with increased genetic [human leukocyte antigen] risk). Secondary prevention refers to the control of autoimmunity in patients who are autoantibody positive; this approach is utilized to halt or delay the immune-mediated destruction of islet cells in order to prevent overt hyperglycemia in patients with pre-clinical T1DM. Last, T1DM intervention represents a management strategy intended to control autoimmunity and preserve remaining  $\beta$ -cell function in patients with clinical disease.

### T1DM Prevention

The potential to effectively interdict the T1DM disease process is believed to be highest in patients with the greatest  $\beta$ -cell mass. As such, overall outcomes are more likely to be successful with prevention than intervention-based strategies. That said, there are many challenges associated with designing and implementing T1DM prevention trials—namely, the need for lengthy, costly clinical trials requiring complex screening procedures, large patient populations, and the use of an investigational agent in patients who may never develop diabetes. Efforts to identify populations of such at-risk individuals are being pursued through TrialNet, a multicenter collaborative clinical research project focused on gaining a greater understanding of the natural history of T1DM, as well as disease prevention and intervention strategies.

Since exposure of healthy patients to high-risk treatments would be unethical, therapeutic agents utilized in T1DM prevention studies, particularly those involving primary prevention, are limited to medications with well-established safety profiles. One of the key agents undergoing investigation for T1DM prevention is the autoantigen insulin. It is proposed that exposure of the gut mucosa, and therefore the immune system, to insulin peptides may help to

*Continued*

**Figure 1. Classification of type 1 diabetes mellitus (T1DM) strategies**

**Primary Prevention**  
prevention of autoimmunity



**Secondary Prevention**  
established autoimmunity;  
prevention of overt hyperglycemia



**Intervention**  
C-peptide preservation;  
not disease reversal

establish tolerance to this islet cell antigen, thereby inhibiting development of autoimmunity in at-risk autoantibody-negative patients and modifying the immune-mediated destruction of  $\beta$ -cells in patients with established autoimmunity (PMID 12951650).

A number of clinical trials have shown promising results with insulin therapy in T1DM prevention. While Diabetes Prevention Trial-Type 1 (DPT-1) investigators failed to show therapeutic efficacy with either oral or parenteral insulin in patients who were islet cell cytoplasmic autoantibody (ICA) positive  $\pm$  insulin autoantibody (IAA) positive with a first- or second-degree relative with T1DM, a post-hoc analysis found that oral insulin appeared to delay disease onset in the subgroup of patients with elevated IAA levels and a 5-year T1DM risk of 25% to 50%. Following nasal insulin therapy in adult patients with antibodies to one or more islet cell antigens, the Australian Intra-nasal Insulin Trial (INIT) I study found

evidence of mucosal tolerance, indicating a potential for immunomodulatory effects that may delay T1DM progression (PMID 15451899).

Ongoing investigations of insulin in primary and secondary prevention of T1DM include a DPT-1 follow-up study, initiated through TrialNet, that will examine the efficacy of oral insulin in delaying T1DM in patients with two or more islet autoantibodies (including IAA); the Primary Oral/Intranasal Insulin Trial (Pre-POINT), a dose-finding study of the preventative effects of oral and intranasal insulin in genetically at-risk but autoantibody-negative infants (PMID 18445349); and the Type 1 Diabetes Prevention Trial (previously called INIT II), a follow-up to INIT I designed to explore the dose-related effects of intranasal insulin on T1DM onset in a larger patient population ([www.diabetestrials.org/initii.html](http://www.diabetestrials.org/initii.html)). Last, although not specific to insulin, the Trial to Reduce IDDM in the Genetically at Risk (TRIGR) has been

designed to examine the hypothesis that weaning to a hydrolyzed formula protects against T1DM initiation and/or progression in genetically at-risk children who have a first-degree relative with T1DM (PMID 17550422).

### Intervention

Compared with T1DM prevention research, intervention studies are likely to involve trials of shorter duration with fewer participants and a more economic screening process (identifying eligible candidates is more straight-forward in patients with overt disease). On the other hand, due to the limited  $\beta$ -cell mass remaining in patients already diagnosed with T1DM, the potential for positive outcomes is reduced in intervention trials. T1DM intervention researchers are also faced with the challenge of defining clinically meaningful markers to assess the success of a particular interdiction. While C-peptide levels have been adopted as the primary surrogate marker in T1DM intervention studies,

*Continued*

**Table 1. Mechanism of action of investigational agents for type 1 diabetes mellitus (T1DM) interdiction**

Agent	Mechanism of action
Glutamic acid decarboxylase 65 (GAD65)	GAD65 therapy may induce immunologic tolerance to this autoantigen, resulting in modulation of the T-cell-mediated destruction of $\beta$ -cells
$\alpha$ 1-antitrypsin (AAT)	AAT protects against $\beta$ -cell apoptosis through inhibition of the caspase-3 enzyme
DiaPep277	DiaPep277 is a peptide derived from the heat shock protein hsp60; it is immunogenic in T1DM patients and may have immune-modulating properties
Anti-CD3	Anti-CD3 monoclonal antibodies act to increase the production of regulatory T-cells believed to be inhibitors of effector T-cell-mediated islet destruction
Anti-CD20	Anti-CD20 monoclonal antibodies down-regulate B lymphocyte signaling of T-cells and may thereby reduce T-cell-mediated islet destruction
Cytotoxic T-lymphocyte antigen-4 immunoglobulin (CTLA-4 Ig)	CTLA-4 Ig is a selective T-cell costimulation modulator with an inhibitory effect on T-cell activation
Anti-thymocyte globulin (ATG)	ATG polyclonal antibody therapy results in non-specific T-cell depletion, which leads to a subsequent rebalancing of effector and regulatory T-cells
Anti-thymocyte globulin (ATG) + granulocyte colony-stimulating factor (GCSF)	ATG provides non-specific T-cell depletion while GCSF stimulates recovery with regulatory T-cells
Autologous umbilical cord blood (UCB) infusion + docosahexaenoic acid (DHA) + vitamin D3	UCB contains a dense population of regulatory T-cells that have potential immunomodulatory effects and may act to limit inflammatory cytokine responses and anergize effector T-cells DHA is an omega-3 fatty acid with anti-inflammatory effects Vitamin D3 provides immunomodulatory activity that may include effects on $\beta$ -cell function, insulin activity, and systemic inflammation
Dendritic cell (DC) therapy	DCs process antigenic material and present it to T-cells, resulting in T-cell activation; modified DCs may have immunosuppressive effect in T1DM
Mesenchymal stem cell (MSC) therapy	MSCs have immunosuppressive and anti-inflammatory properties and may have B- and T-cell antiproliferative effects

investigators have yet to translate such measurements into clinically relevant outcomes such as reductions in A1C levels, lower insulin requirements, or fewer diabetes-related complications.

A range of immunosuppressive and immunomodulatory medications has been investigated for control of autoimmunity and preservation of  $\beta$ -cell function in T1DM. While some have been hindered by limited efficacy and/or safety/tolerability concerns, others have shown promise, including a number of medications used in the treatment of other immune-mediated conditions. Among the immunoregulatory agents currently being investigated for efficacy in T1DM intervention are the autoantigen glutamic acid decarboxylase 65 and a number of non-antigen specific therapies, including DiaPep277, anti-CD3, and anti-CD20 monoclonal antibodies;  $\alpha$ 1-antitrypsin; cytotoxic T-lymphocyte antigen-4 immunoglobulin; anti-thymocyte globulin+granulocyte

colony-stimulating factor; autologous umbilical cord blood infusion combined with docosahexaenoic acid and vitamin D3; dendritic cells; and mesenchymal stem cell therapy. Table 1 on the previous page provides a summary of the proposed mechanisms of action for each of these compounds.

### Recent, Ongoing, and Forthcoming Clinical Research

Ongoing research efforts to explore new therapeutic modalities for T1DM prevention and intervention are guided by the findings of previous research. Key clinical findings from completed studies of investigational T1DM compounds are described in Table 2.

Table 3 (next page) provides a summary of key ongoing and forthcoming T1DM clinical research using investigational compounds; studies are classified according to whether the agent being investigated is for primary prevention, secondary prevention, or intervention.

### Future Directions

Given the considerable heterogeneity of T1DM, its successful prevention and cure will likely require development of therapies that employ an appropriate balance between risk and potential benefits. Agents with immunomodulatory and perhaps immunosuppressive effects will be necessary to achieve success in prevention and early intervention trials, while the addition of therapies with the potential to induce  $\beta$ -cell regeneration will be vital to achieve disease reversal in patients with established T1DM.

Given the complexity of the T1DM disease process and the limited success obtained thus far with monotherapy, evidence suggests that combination therapy will likely be the best approach to T1DM interdiction. This strategy has the potential to act on multiple targets with potentially synergistic mechanisms of action.

*Continued*

**Table 2. Recently completed type 1 diabetes mellitus (T1DM) clinical research studies**

Type of interdiction / agent	Clinical studies
<b>Secondary prevention</b>	
Insulin	Finnish Diabetes Prediction and Prevention Project (DIPP) failed to demonstrate efficacy of intranasal insulin in genetically at-risk autoantibody-positive patients (N=20) ( <a href="#">PMID 12951650</a> )
<b>Intervention</b>	
Glutamic acid decarboxylase 65 (GAD65)	Randomized double-blind phase II study in children with T1DM (N=70) found that GAD65 therapy resulted in increases in both fasting and stimulated C-peptide levels and may therefore preserve endogenous $\beta$ -cell function ( <a href="#">PMID 18843118</a> )
DiaPep277	Randomized double-blind phase Ib/II trial in patients with recent-onset T1DM (N=48) showed that DiaPep277 immunization may lead to C-peptide preservation ( <a href="#">PMID 18422727</a> )
Anti-CD3 monoclonal antibodies	Two randomized phase II studies in patients with recent-onset T1DM (N=80 and N=10) reported preservation of residual $\beta$ -cell function (based on C-peptide measurements) for 18-24 months following short-term anti-CD3 therapy ( <a href="#">PMID 15972866</a> ; <a href="#">19443276</a> )
Anti-CD20 monoclonal antibodies	Randomized placebo-controlled TrialNet study demonstrated C-peptide preservation 1 year after IV infusion with anti-CD20 therapy in patients with recent-onset T1DM (N=87); 2-year data yet to be reported ( <a href="#">PMID 19940299</a> )
Mycophenolate mofetil (MMF) $\pm$ daclizumab (DZB)	Multicenter, randomized, placebo-controlled, double-blind TrialNet study of patients with new-onset T1DM (N=126) showed no effect on C-peptide levels with MMF alone or in combination with DZB ( <a href="#">PMID 20067954</a> )
Anti-thymocyte globulin (ATG)	Prospective, randomized, controlled, parallel-group pilot study of ATG therapy in patients with recent-onset T1DM (N=30) reported C-peptide preservation and reduction of insulin requirements at 1 year, with acceptable tolerability results ( <a href="#">PMID 17491669</a> )
Anti-thymocyte globulin (ATG) + granulocyte colony-stimulating factor (GCSF) + cyclophosphamide	Prospective phase I/II study of ATG/GCSF/cyclophosphamide therapy (also called autologous nonmyeloablative hematopoietic stem cell transplantation) in young adults with newly diagnosed T1DM (N=23) demonstrated increased C-peptide levels and, for a majority of patients, insulin independence for $\geq 1$ year, although a high morbidity rate led to safety concerns ( <a href="#">PMID 19366777</a> )

Further, use of multiple agents at lower doses may achieve higher efficacy with a reduced risk of adverse effects; the success of similar approaches has been demonstrated in both cancer and HIV treatment. “Cocktail” therapies currently being investigated in T1DM include anti-thymocyte globulin/granu-

loocyte colony-stimulating factor and autologous umbilical cord blood/ docosahexaenoic acid/vitamin D3.

As new T1DM treatment modalities are explored, some important factors to consider during trial design include identifying target patient populations,

screening requirements, ease of agent administration, existing efficacy and safety data, and cost. Whereas strategies for T1DM prevention, particularly those used in children, must be low risk (eg, autologous umbilical cord blood infusion/docosahexaenoic acid/vitamin

*Continued*

**Table 3. Ongoing and forthcoming type 1 diabetes mellitus (T1DM) clinical research studies**

Type of intervention / agent	Clinical studies	Status
<b>Primary prevention</b>		
Insulin	Primary Oral/Intranasal Insulin Trial (Pre-POINT) – Dose-finding pilot study of oral and intranasal insulin for T1DM prevention in genetically at-risk but autoantibody-negative infants ( <a href="http://www.diabetes-point.org/nav2uk.html">www.diabetes-point.org/nav2uk.html</a> )	Ongoing
Avoidance of cow milk protein	Trial to Reduce IDDM in the Genetically at Risk (TRIGR) – Multicenter, international, prospective, double-blind, placebo-controlled study examining the hypothesis that weaning infants to a hydrolyzed formula protects against T1DM initiation/progression in genetically at-risk children who have a first-degree relative with T1DM ( <a href="http://www.trignorthamerica.org">www.trignorthamerica.org</a> )	Ongoing
<b>Secondary prevention</b>		
Insulin	Oral Insulin for the Prevention of Type 1 Diabetes Trial (TrialNet) – DPT-1 follow-up study of oral insulin for delay of T1DM onset in intermediate-risk patients with $\geq 2$ islet autoantibodies (including IAAsulin autoantibody) ( <a href="http://www.diabetestrialnet.org/index.htm">www.diabetestrialnet.org/index.htm</a> )	Ongoing
	Type 1 Diabetes Prevention Trial (previously called INIT II) – Study of dose-related efficacy of intranasal insulin for T1DM prevention in patients with antibodies to $\geq 1$ islet cell antigens and a first-degree relative with T1DM ( <a href="http://www.diabetestrials.org/initii.html">www.diabetestrials.org/initii.html</a> and <a href="http://www.stopdiabetes.com.au">www.stopdiabetes.com.au</a> )	Ongoing
Anti-CD3 Monoclonal Antibodies	TrialNet – Study of anti-CD3 administered by IV infusion for T1DM prevention in very high-risk patients with $\geq 2$ islet autoantibodies, evidence of impaired glucose tolerance, and a relative with T1DM ( <a href="http://www.diabetestrialnet.org/index.htm">www.diabetestrialnet.org/index.htm</a> ) Note: Dosing regimens require 6- to 14-day IV infusion; potential safety issues include cytokine release syndrome following initial dosing, Epstein-Barr virus reactivation, and formation of anti-CD3 antibodies	Forthcoming
<b>Intervention</b>		
Glutamic Acid Decarboxylase 65 (GAD65)	DiaPrevent (TrialNet) – Phase III study of GAD65 administered via subcutaneous injection as T1DM intervention in newly diagnosed patients ( <a href="http://www.diabetestrialnet.org/index.htm">www.diabetestrialnet.org/index.htm</a> and <a href="http://www.diaprevent.diamyd.com/Default.aspx?referrer=1">www.diaprevent.diamyd.com/Default.aspx?referrer=1</a> )	Ongoing
Anti-CD20 Monoclonal Antibodies	TrialNet – Randomized placebo-controlled study demonstrated C-peptide preservation 1 year after IV infusion with anti-CD20 therapy in patients with recent-onset T1DM (N=87); 2-year data yet to be reported (PMID 19940299) Note: Anti-CD20 (rituximab) has demonstrated benefit in other human autoimmune diseases such as rheumatoid arthritis and non-Hodgkin’s lymphoma and has shown promise in the treatment of lupus and multiple sclerosis	Ongoing
Cytotoxic T-Lymphocyte Antigen-4 Immunoglobulin (CTLA-4 Ig)	TrialNet – Randomized, double-blind, placebo-controlled study of CTLA-4 Ig administered by IV infusion in recently diagnosed T1DM patients ( <a href="http://www.diabetestrialnet.org/index.htm">www.diabetestrialnet.org/index.htm</a> ) Notes: CTLA-4 Ig (abatacept) is FDA-approved for the treatment of rheumatoid arthritis; enrollment completed in 2009, results expected in 2011	Ongoing
Anti-thymocyte globulin (ATG)	Study of Thymoglobulin to Arrest Type 1 Diabetes (START) trial – Conducted by the Immune Tolerance Network to investigate ATG in recently diagnosed T1DM patients ( <a href="http://www.immunetolerance.org">www.immunetolerance.org</a> and <a href="http://www.type1diabetestrial.org">www.type1diabetestrial.org</a> )	Ongoing
ATG + granulocyte colony-stimulating factor (GCSF)	Study of ATG/GCSF efficacy and safety as T1DM intervention; based on promising preclinical data	Ongoing
Autologous umbilical cord blood (UCB) infusion	Phase I trial of autologous UCB infusion. Awaiting 2-year data regarding efficacy in C-peptide preservation in young children with T1DM	Ongoing
	Phase II study of autologous UCB infusion followed by 1-year supplementation with docosahexaenoic acid (DHA) and vitamin D3 to assess efficacy in C-peptide preservation	Ongoing
Dendritic cell (DC) therapy	Phase I study of autologous modified DC therapy in patients with T1DM (PMID 18552749)	Ongoing
Mesenchymal stem cell (MSC) therapy	Randomized, double-blind, placebo-controlled phase II study of MSC safety and efficacy in patients with new-onset T1DM (N=60) ( <a href="http://www.osiris.com/clinical_prochymal_t1dm.php">www.osiris.com/clinical_prochymal_t1dm.php</a> )	Ongoing

D3, avoidance of cow milk proteins), higher-risk intervention therapy (eg, autologous nonmyeloablative hematopoietic stem cell transplantation) may be considered in adults with established disease. In all situations, the limited availability of both human and financial resources makes it critical that researchers be selective as they pursue future T1DM studies.

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### Suggested Reading

Haller MJ, Atkinson MA, Schatz DA. The road not taken: a path to curing type 1 diabetes? *Eur J Immunol.* 2009;39:2054-2058.

Haller MJ, Atkinson MA, Schatz D. Type 1 diabetes mellitus: etiology, presentation, and management. *Pediatr Clin North Am.* 2005; 52:1553-1578.

Haller MJ, Gottlieb PA, Schatz DA. Type 1 diabetes intervention trials 2007: where are we and where are we going? *Curr Opin Endocrinol Diabetes Obes.* 2007;14:283-287.

Kishiyama CM, Chase HP, Barker JM. Prevention strategies for type 1 diabetes. *Rev Endocr Metab Disord.* 2006;7:215-224.

Rewers M, Gottlieb P. Immunotherapy for the prevention and treatment of type 1 diabetes: human trials and a look into the future. *Diabetes Care.* 2009;32:1769-1782.

Skyler JS for the Type 1 Diabetes TrialNet Study Group. Update on worldwide efforts to prevent type 1 diabetes. *Ann N Y Acad Sci.* 2008;1150: 190-196.

Staeva-Vieira T, Peakman M, vonHerrath M. Translational mini-review series on type 1 diabetes: immune-based therapeutic approaches for type 1 diabetes. *Clin Exp Immunol.* 2007;148:17-31.

## LITERATURE CORNER

### ROLE OF OBESITY IN THE DEVELOPMENT OF TYPE 2 DIABETES IN YOUTH

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#### Introduction

In this article, we discuss the role of obesity in the development of type 2 diabetes mellitus (T2DM) in the pediatric population. For children and adolescents, the US Centers for Disease Control and Prevention uses the terms "at risk of overweight" and "overweight" to represent the 85th to <95th percentiles and the ≥95th percentiles of sex-specific body mass index (BMI) for age, respectively, while the International Obesity Task Force and the Institute of Medicine use "overweight" and "obese" to describe these two categories (click on the PubMed ID number to read more: [PMID 18055651](#)).

#### The Epidemic of Childhood Obesity

The 2003-2004 National Health and Nutrition Examination Survey (NHANES) estimated that one-third of the children in the United States are overweight or

obese. Between 1980 and 2002, the prevalence of obesity more than tripled in children and adolescents aged 6 to 19 years. Although the most recent data (NHANES 2003-2004 to 2005-2006) found no increase in the prevalence of childhood overweight or obesity, it is probably too early to say whether this represents a true plateau ([PMID 18505949](#)).

Rates of abdominal obesity are also increasing. Using data obtained from NHANES 1988-1994 and 1999-2004, trends in waist circumference among US children and adolescents indicate increased abdominal girth in black, white, and Hispanic youth aged 2 to 19 years. Data are similar for British youth. The increased prevalence of childhood obesity in the United States is mirrored internationally in many developed and developing countries; worldwide, about 110 million children are classified as overweight or obese ([PMID 16198769](#)).

#### Metabolic Consequences of Childhood Obesity

Overweight and obesity are associated with serious medical, psychological, and social consequences throughout the life span. In addition, childhood obesity frequently persists into adulthood. The Bogalusa Heart Study demonstrated that, among obese youth, 77% remained obese adults ([PMID 11533341](#)). Furthermore, many metabolic complications of obesity, such as dyslipidemia and hyperinsulinemia, are already present during childhood; these are closely related to insulin resistance driven by abdominal obesity ([PMID 17475936](#)).

Although overweight and obesity are independently associated with insulin resistance, body fat distribution also plays an important role. Our research indicates that, among obese adolescents with comparable BMIs, those with greater amounts of visceral fat (measured by computed tomography) were more insulin resistant, regardless of race. We subsequently determined that applying waist circumference as a surrogate measure for abdominal adiposity independently explained 55%

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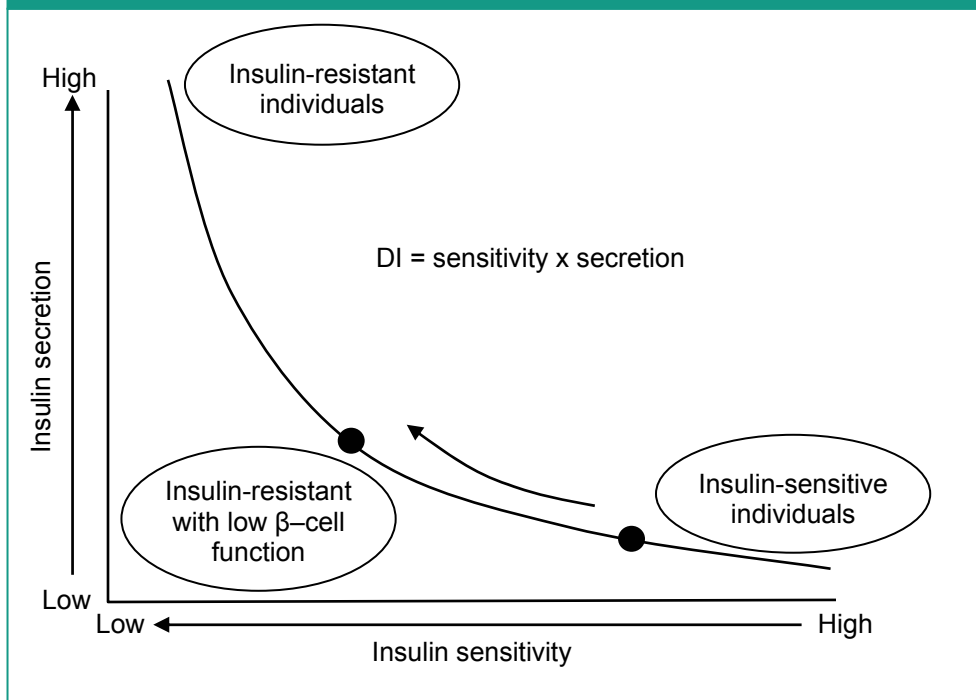
of the overall variance in insulin sensitivity observed between black and white youth ([PMID 16492427](#)).

The contributions of total and visceral fat to insulin resistance varies with ethnicity. Data for Hispanic children suggest that both total and visceral fat contribute independently to reduced insulin sensitivity ([PMID 12196439](#)). In a study we conducted in overweight children with similar BMIs, total body fat, and percent body fat, black children had ~30% less visceral fat than white children. Higher visceral fat in blacks was associated with increased diabetogenic risk, while in whites it was associated with increased atherogenic risk ([PMID 12788850](#)). Moreover, levels of adiponectin, an antidiabetogenic and antiatherogenic hormone, were positively associated with insulin sensitivity; therefore, the low adiponectin levels observed in black versus white youth might indicate a greater risk of or predisposition to insulin resistance ([PMID 16373895](#)).

**Pathophysiology of Type 2 Diabetes in Youth: Insulin Sensitivity and Secretion**

In children and adults, glucose homeostasis is maintained through a delicate balance between peripheral and hepatic insulin sensitivity, alongside insulin secretion from pancreatic  $\beta$ -cells. In healthy individuals, the relationship between insulin sensitivity and secretion is best described as a hyperbolic function (Figure 1) ([PMID 16439840](#); [11815482](#)). This indicates that the product of insulin sensitivity and  $\beta$ -cell function (termed the disposition index or insulin secretion relative to insulin sensitivity) is a constant for a given level of glucose tolerance. It also implies that a feedback loop governs interactions between the  $\beta$ -cells and peripheral tissues. Thus, when insulin sensitivity decreases, as is the case in obesity, insulin secretion must increase for glucose tolerance to remain constant. If this compensatory increase in insulin secretion is incomplete, a mild deterioration in glucose tolerance occurs; over time, this may progress to overt diabetes.

**Figure 1. Hyperbolic relationship between insulin sensitivity and secretion**



DI, disposition index  
From Arslanian SA. *Horm Res.* 2005;64(Suppl 3):16-24; used with permission.

Another implication of this hyperbolic function is that although insulin secretion may be identical in two individuals, if insulin sensitivity is different, then glucose tolerance will differ. Not surprisingly, our research shows that obese adolescents who are severely insulin resistant are at greater risk for T2DM compared with their peers who are moderately insulin resistant ([PMID 16801585](#)).

**The contributions of total and visceral fat to insulin resistance varies with ethnicity.**

Limited cross-sectional studies in children confirm that T2DM is characterized by impaired insulin secretion against a backdrop of insulin resistance. Our group has demonstrated that insulin sensitivity is ~50% lower in obese adolescents with T2DM compared with equally obese non-diabetic controls; however, in youth

with T2DM, first-phase insulin secretion is also severely impaired (~75% lower) ([PMID 15735201](#)). Such abnormalities are also observed, though to a lesser degree, in obese adolescents with impaired glucose tolerance (IGT) ([PMID 14511928](#); [15919795](#)).

Our research in obese, normal-glucose tolerant (NGT) versus IGT versus T2DM adolescents demonstrates that the disposition index shows a declining pattern that is highest in NGT, intermediate in IGT, and lowest in T2DM ([PMID 18835946](#)). In high-risk overweight Latino children, impaired fasting glucose (IFG) was associated with an ~15% lower disposition index compared with NGT children ([PMID 16186290](#)). In another study of obese adolescents, model-derived insulin secretion parameters were lower in IFG (by 38%) and IGT (by 23%), even though absolute values of first- and second-phase insulin release did not differ ([PMID 18303080](#)).

In light of the above observations, a proposed stepwise pathophysiology of

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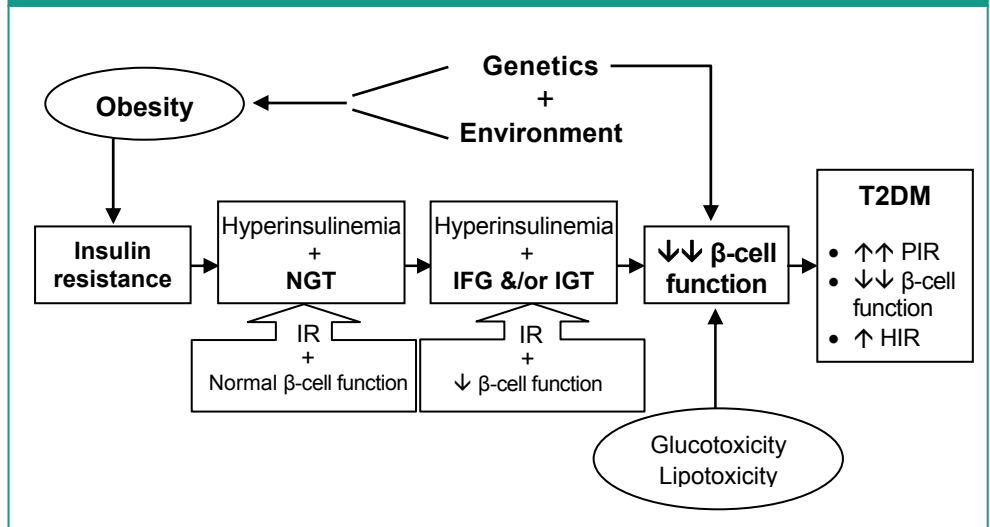
T2DM is outlined in Figure 2. We suggest that the earliest abnormality is insulin resistance, driven mostly by obesity, which over time progresses to T2DM in individuals genetically and/or environmentally predisposed to  $\beta$ -cell failure ([PMID 11202214](#); [17008794](#); [16061606](#); [18316946](#)).

### Frequency of T2DM In Youth

A number of studies report escalating proportions of youth with T2DM, particularly in certain racial/ethnic populations ([PMID 9726592](#); [11994905](#); [8627431](#)). The SEARCH for Diabetes in Youth Study reported incidence estimates from 10 geographically distinct US sites for 2002 to 2003 by age group, sex, and race/ethnicity ([PMID 17595272](#)). Overall, incidence of T2DM was relatively low, with the highest rates (17.0 to 49.4 per 100,000 person-years) observed among 15- to 19-year-old minority groups. As a proportional distribution of all diabetes cases, T2DM was most common among minorities aged 10 to 19 years, especially American Indian (86.2%), Asian/Pacific Islander (69.7%), African American (57.8%), and Hispanic (46.1%) youth. Although SEARCH data support the notion that T2DM in youth predominantly occurs in high-risk ethnic groups, T2DM still accounted for 14.9% of all diabetes mellitus cases among white adolescents aged 10 to 19 years. Despite these figures, in absolute terms, the number of youth with T2DM in the United States is low, with the total number of cases among individuals <20 years of age estimated at 39,000 ([PMID 17595278](#)).

Increased rates of T2DM in youths are also reflected internationally. In Japan, 80% of all new cases of diabetes in children and adolescents are diagnosed as T2DM, and from 1976 to 1995 the T2DM incidence rate among Japanese primary school children in Tokyo increased 10-fold ([PMID 15870677](#)). This increase was paralleled by increases in childhood and adolescent obesity and a shift from the traditional Japanese diet to consumption of more animal fat and protein ([PMID 9492119](#)). The problem is not isolated to the Asia-Pacific region,

**Figure 2. Proposed metabolic stages in the progression from obesity to type 2 diabetes mellitus (T2DM) in youth**



HIR, hepatic insulin resistance; IR, insulin resistance; PIR, peripheral insulin resistance  
Adapted and modified with permission from Arslanian SA. *J Pediatr Endocrinol Metab.* 2000; 13(Suppl 6):1385-1394.

however, and similar reports exist for Europe, South America, and the Middle East. As in the United States, T2DM seems to manifest predominantly in non-Caucasians — the first youth identified in the United Kingdom were of Pakistani, Indian, and Arabic origin ([PMID 11168330](#)).

### Screening At-Risk Obese Children for T2DM

With increased rates of childhood obesity and T2DM, screening at-risk obese youth is of paramount importance. Screening enables the early identification and treatment of the disease, which is critical since T2DM is often asymptomatic. Furthermore, the early identification of pre-diabetes (IFG and/or IGT) can provide a basis to recommend lifestyle intervention, which, based on studies conducted in adults, may prevent progression to T2DM ([PMID 17237299](#)). Both the American Diabetes Association (ADA) and the International Diabetes Federation (IDF) ([PMID 10868870](#); [15220270](#); respectively) recommend screening overweight or obese children and adolescents with  $\geq 1$  additional risk factors (Table 1, next page). The ADA recommends screening using fasting glucose, whereas the IDF recommends the oral glucose tolerance test (OGTT). Our studies of

OGTT in obese youth reveal that, among individuals with IGT, only 30% have abnormal fasting glucose consistent with IFG ([PMID 18713820](#)). Thus, screening using fasting glucose could miss a substantial proportion of IGT in obese youth. Therefore, we agree with the IDF that screening should be conducted using OGTT, especially in high-risk children.

### Pre-diabetes in Obese Children

The prevalence of pre-diabetes, defined as IFG, IGT, or both, varies greatly among populations. In the United States, the overall prevalence of IFG in a nationally representative sample of adolescents 12 to 19 years old was 7.0% (NHANES 1999-2000). This figure was much higher in overweight adolescents (17.8%) and varied significantly across racial/ethnic groups ([PMID 16263998](#)). In the NHANES 1999-2002 sample, 0.5% of youth had diabetes (29% of those cases were categorized as T2DM), and roughly 11% had IFG ([PMID 16651496](#)). These proportions were equivalent to 39,005 US adolescents with T2DM and 2,769,736 with IFG. In NHANES 2005-2006, the unadjusted prevalence of IFG, IGT, and pre-diabetes was 13.1%, 3.4%, and 16.1%, respectively, and overweight adolescents had a 2.6-fold

Continued

higher risk than those with normal weight (PMID 18957533). In specialty obesity referral clinics, the reported rates of IGT are much higher, at 25% in obese 4- to 10-year-old children and 21% in obese 11 to 18 year olds. In our experience with overweight/obese 8- to 17-year-old research participants, the prevalence of IFG ranged from 5% to 10% and IGT was ~20%. Similar to these wide variations in IFG and IGT rates, the reported conversion rates from IGT to T2DM vary widely (ranging from 0% to 24%) (PMID 18678615; 15793193). Such wide variations in prevalence and conversion could be attributed to the poor reproducibility of the OGTT in overweight youth (PMID 18713820), in addition to differences in population characteristics.

### Summary

The steep trajectory of obesity is the trigger for the rising rates of T2DM in youth at genetic/epigenetic risk. Obesity, particularly visceral adiposity,

leads to impaired whole-body insulin sensitivity, resulting in insulin resistance at an early age. When this is combined with defective  $\beta$ -cell function, pre-diabetes and/or T2DM are likely to occur. Thus, overweight/obese children with a family history of T2DM, particularly those from ethnic minorities, should be regularly screened for the presence of pre-diabetes or undiagnosed T2DM. More importantly, the tide of T2DM will not be reversed until public health efforts are implemented to prevent obesity at the population level.

*Dr. Burns and Dr. Arslanian have no commercial relationships to disclose related to the content of this article.*

### Suggested Reading

Alberti G, Zimmet P, Shaw J, et al. Type 2 diabetes in the young: the evolving epidemic: the International Diabetes Federation Consensus Workshop. *Diabetes Care*. 2004;27:1798-1811.

Bacha F, Arslanian S. Insulin resistance and insulin secretion in the pathophysiology of youth type 2 diabetes. In: Dabelea D, Klingensmith G, eds. *Epidemiology of Pediatric and Adolescent Diabetes*. New York, NY: Informa Healthcare USA, Inc; 2008:139-155.

Bergman RN, Ader M, Huecking K, Van Citters G. Accurate assessment of beta-cell function: the hyperbolic correction. *Diabetes*. 2002; 51:S212-S220.

Candido C, Bacha F, Hannon T, et al. Obesity and type 2 diabetes. In: Lebovitz H, ed. *Therapy of Diabetes Mellitus and Related Disorders*. 5th ed. Alexandria, VA: American Diabetes Association; 2009.

Lee S, Bacha F, Gungor N, Arslanian SA. Waist circumference is an independent predictor of insulin resistance in black and white youths. *J Pediatr*. 2006;148:188-194.

Ogden CL, Carroll MD, Curtin LR, et al. Prevalence of overweight and obesity in the United States, 1999-2004. *JAMA*. 2006;295:1549-1555.

Type 2 diabetes in children and adolescents. American Diabetes Association. *Diabetes Care*. 2000;23:381-389.

Writing Group for the SEARCH for Diabetes in Youth Study Group. Incidence of diabetes in youth in the United States. *JAMA*. 2007; 297:2716-2724.

**Table 1. Risk factors, features, and screening guidelines for type 2 diabetes mellitus (T2DM) in youth**

American Diabetes Association (ADA)	International Diabetes Federation (IDF)
<ul style="list-style-type: none"> <li>• <b>Criteria</b><sup>1</sup> <ul style="list-style-type: none"> <li>Overweight and obesity</li> <li>BMI &gt;85th percentile for age and gender</li> <li><b>or</b></li> <li>Body weight for height &gt;85th percentile</li> <li><b>or</b></li> <li>Body weight &gt;120% of ideal for height</li> <li>Plus any two of the following                             <ul style="list-style-type: none"> <li>Family history of T2DM in first- or second-degree relatives</li> <li>Race/ethnicity (American Indian, Black, Hispanic, Asian/Pacific Islander)</li> <li>Signs of insulin resistance or conditions associated with insulin resistance (acanthosis nigricans, hypertension, dyslipidemia, polycystic ovary syndrome)</li> </ul> </li> </ul> </li> <li>• <b>Age of screening initiation</b> <ul style="list-style-type: none"> <li>10 years or at onset of puberty if puberty occurs at a younger age</li> </ul> </li> <li>• <b>Frequency of testing</b> <ul style="list-style-type: none"> <li>Every 2 years</li> </ul> </li> <li>• <b>Test</b> <ul style="list-style-type: none"> <li>Fasting plasma glucose</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• <b>Onset</b> <ul style="list-style-type: none"> <li>Slow — often asymptomatic</li> </ul> </li> <li>• <b>Clinical picture</b> <ul style="list-style-type: none"> <li>Obesity</li> <li>Strong family history of T2DM</li> <li>Ethnicity — high-prevalence populations</li> <li>Acanthosis nigricans</li> <li>Signs of insulin resistance</li> <li>Polycystic ovary syndrome</li> <li>Intrauterine environment — low birth weight or gestational diabetes</li> <li>Physical inactivity</li> <li>Sex — girls more likely than boys</li> </ul> </li> <li>• <b>Ketosis</b> <ul style="list-style-type: none"> <li>Usually absent</li> </ul> </li> <li>• <b>Insulin</b> <ul style="list-style-type: none"> <li>C-peptide positive</li> </ul> </li> <li>• <b>Antibodies</b> <ul style="list-style-type: none"> <li>ICA negative</li> <li>Anti-GAD negative</li> <li>ICA 512 negative</li> </ul> </li> <li>• <b>Test</b> <ul style="list-style-type: none"> <li>Oral glucose tolerance test</li> </ul> </li> </ul>

<sup>1</sup>Clinical judgment should be used to test for diabetes in high-risk patients who do not meet these criteria Adapted from ADA. *Diabetes Care*. 2000;23:381-389; IDF. *Diabetes Care*. 2004;27:1798-1811.