

GOAL IV:

PREVENT OR REDUCE HYPOGLYCEMIA IN TYPE 1 DIABETES

Why It Is Important To Prevent or Reduce Hypoglycemia In Type 1 Diabetes

- Sensing Low Blood Glucose
- Preventing Hypoglycemia-Associated Autonomic Failure (HAAF)
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WHY IT IS IMPORTANT TO PREVENT OR REDUCE HYPOGLYCEMIA IN TYPE 1 DIABETES

Patients with type 1 diabetes walk a tightrope. Every time they check their blood glucose and adjust their insulin, they must balance the immediate danger of low blood glucose and the long-term risk of complications from high blood glucose. They worry, “What if insulin therapy makes my blood glucose level drop dangerously low and I’m not even aware of it? Will I go into a life-threatening coma as a result? Who will even know this is happening, and will they be able to help me?” Similar questions haunt the parents of young children with diabetes—many of whom cannot sleep at night because they are standing watch at their child’s bedside. Facing an episode of dangerously low blood glucose—known as hypoglycemia—is one of the greatest fears of patients with type 1 diabetes and their families. Thus, an urgent research goal is to find ways to prevent or reduce this acute danger of insulin treatment.

Insulin therapy is a life-saving treatment for people with type 1 diabetes. However, it is sometimes difficult for patients to gauge the exact amount of insulin that they should administer to themselves at any given moment to meet their body’s needs. Some patients use pumps that deliver insulin, but these devices have not yet been developed to the point where they can sense and respond to the body’s need for insulin.

If there is too much insulin in the body, it increases the risk of hypoglycemia, or low blood glucose. When blood glucose levels fall below a minimal threshold, serious and life-threatening consequences can result. Moreover, after a few episodes of hypoglycemia, patients with type 1 diabetes can lose the ability to sense drops in blood glucose levels, a condition called hypoglycemia unawareness. Therefore, they are at increased risk of additional hypoglycemic episodes. This risk is even greater at night, especially for children, causing anxious parents to go without sleep themselves so they can monitor their children for signs of low blood glucose levels. Adults with type 1 diabetes also worry about hypoglycemia unawareness. Those who have ever experienced severe low blood glucose episodes are especially fearful. Unfortunately, these fears can lead them to abandon a regimen of intensive management, even though research has demonstrated its benefit in preventing or delaying the heart, eye, nerve, and kidney complications of diabetes. Clearly, research that leads to new or better ways to prevent or reduce low blood glucose could profoundly improve the health and well-being of people with type 1 diabetes and their families.

Researchers are attacking the problem of low blood glucose from several angles. They aim to understand how the body and brain normally communicate about blood glucose levels, as well as to identify what parts of this communication network are damaged or impaired in people with type 1 diabetes. An important tool for research in these critical areas will be animal models of disease. Through a multifaceted approach, researchers hope to more rapidly achieve the ultimate goal of preventing or reducing hypoglycemia in patients with type 1 diabetes. They are asking several questions: How do recurring hypoglycemic episodes impair a patient’s awareness of impending low blood glucose levels and resulting hormonal responses over time—a vicious cycle called “hypoglycemia-associated autonomic failure,” or HAAF? How can a patient’s brain adapt to protect itself from low blood glucose damage? What new clinical approaches would minimize the risk of low blood glucose, such as technologies that could integrate glucose level sensing and insulin delivery? Can effective educational, behavioral, and clinical strategies be developed to prevent or reduce hypoglycemic episodes?

Sensing Low Blood Glucose

Understanding how the brain and body work together to determine and adjust blood glucose levels is a complex undertaking, but researchers have made significant progress in the past decade. Scientists now know that glucose-sensing cells are stationed within the brain and in key blood vessels outside of the brain that pick up signals and send them to the brain.

They also know more about how those cells are “wired” to the brain, so that it can receive continuous information about blood glucose levels. New insights are emerging about how the brain integrates this input with other metabolic signals it receives to develop the best response to keep blood glucose levels in a normal range.

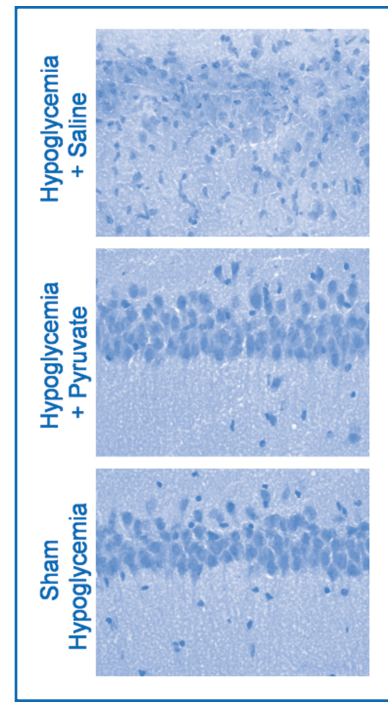
Now that researchers have a big picture, they are seeking the details of the body’s sensing apparatus and how it is affected by having type 1 diabetes. The underlying disease and insulin therapy may also alter the levels of other metabolic signals, thereby affecting how the brain responds to signals of low blood glucose levels. By identifying the mechanisms and other factors involved, researchers will be better positioned to develop effective clinical interventions to prevent precipitous drops in blood glucose in patients. Already, blood glucose awareness training for patients with type 1 diabetes has demonstrated dramatic benefits. Patients improved in their ability to detect high and low blood glucose levels and adjust their glucose accordingly. It is important to find ways to disseminate and implement these positive findings so that more patients can benefit.

Preventing Hypoglycemia-Associated Autonomic Failure (HAAF)

What contributes to the recurring nature of hypoglycemic episodes and increasing unawareness that an episode is about to strike? Normally, a drop in blood glucose triggers the body’s warning system to release stress hormones, including adrenaline, and to stimulate a part of the nervous system that raises glucose and results in such symptoms as nervousness, shaking, and sweating. These warning symptoms help make people aware that they need to eat or take other steps to increase their blood glucose levels. The body also reacts with other “counter-regulation” defense measures, including the release of a hormone that elevates blood glucose (glucagon). However, in people with type 1 diabetes, these alert mechanisms and defense measures are significantly impaired and worsen with each episode of low blood glucose.

Being unaware of plummeting blood glucose levels is both dangerous and frightening. Moreover, patients are faced with the difficult fact that using insulin therapy to tightly control blood glucose levels and improve health in the long term increases their risk of severe and worsening low blood glucose episodes in the short term. Although the HAAF syndrome can be reversed by as little as several weeks of scrupulous avoidance of low blood glucose levels, it is difficult to accomplish this without losing good control of blood glucose levels and, thus, losing the benefits of this control, such as preventing long-term complications. Thus, it is critically important to identify the as-yet unknown mechanisms responsible for

Severe hypoglycemia can lead to death of neurons in the brain. In one study, hypoglycemia was induced in rats (top 2 panels) but not induced in the control rats (bottom panel). Hypoglycemia was terminated by treatment with glucose alone (top panel) or glucose plus pyruvate (middle panel). Analysis of hippocampal brain sections 7 weeks after the hypoglycemic injury showed that the rats treated with glucose plus pyruvate had less neuronal death than rats treated with glucose alone, suggesting that pyruvate may protect neurons from death due to severe hypoglycemia.



(Image courtesy of Dr. Raymond Swanson.

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hypoglycemia unawareness so that new clinical strategies can be developed to combat HAAF, while simultaneously improving or maintaining good blood glucose control.

Future research will be focused on new strategies to prevent or reverse the HAAF syndrome. To do this, researchers will need to focus on three major objectives. First, they will need to identify how low blood glucose causes HAAF to develop, by studying this syndrome in animals. Animal models will also be important for research that can lead to preventive therapies. Second, researchers will need to use multiple tools to study what is happening in the brains and bodies of people affected by HAAF and how it affects their management of diabetes. For example, brain imaging studies combined with hormone measurements could help researchers understand why patients are so vulnerable to hypoglycemia while they sleep or when they need to perform complex tasks. Finally, studies should focus on ways to restore the body’s innate ability to counter low blood glucose levels with defense mechanisms that elevate blood glucose.

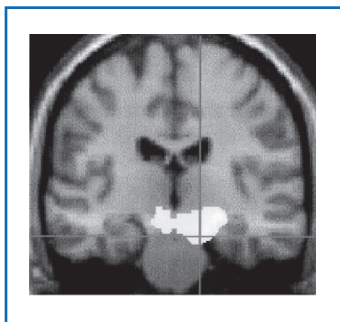
Protecting the Brain

The brain is almost entirely dependent upon blood glucose for the energy it needs to work. This dependency makes the brain quite vulnerable to episodes of low blood glucose. While it is crucial to discover ways to prevent these episodes in the

first place, it is equally important to pursue therapies that patients can use to protect the brain from injury due to low blood glucose.

Developing effective new therapies will require knowledge of how the brain acts to obtain a constant fuel supply, and what it does to protect itself when its major fuel, glucose, is in short supply. Studies are providing insights about the alternate fuels and fuel reserves that the brain uses when blood glucose is in short supply and are showing that patients with type 1 diabetes may use alternate fuels more efficiently. More is now known about how glucose and other fuels move from the blood into the brain. Now, emphasis needs to be placed on identifying the specific changes that occur in the brain in the face of low blood glucose and on determining which of these are the most important to exploit for therapeutic intervention—both to reverse brain injury and to promote protection from brain injury. For example, if use of alternate fuels is an effective way for the brain to protect itself from injury, then patients could take agents to increase those fuel supplies.

It appears that the brain's mechanisms for enhancing fuel efficiency and protecting itself from injury create a catch-22 situation—while protecting the brain from immediate injury, they seemingly “hide” low blood glucose levels from the



The image depicts a composite analysis of brain imaging studies of type 1 diabetes patients with or without hypoglycemia unawareness, at either normal or low glucose levels. The white portion represents an area of the brain known to contain glucose-sensing cells in which differences in the uptake of a labeled form of glucose is observed in the two patient populations.

Patients with hypoglycemia unawareness had lower glucose uptake. These data suggest altered glucose uptake, metabolism, or both, in this brain region, which is associated with hypoglycemia unawareness.

(Image courtesy of Drs. Stephanie Amiel and Laurence John Reed. Copyright © 2001 American Diabetes Association. From Diabetes, Vol. 50, 2001; 2329-2336. Reprinted with permission from The American Diabetes Association.)

patient, contributing to hypoglycemia unawareness. During a hypoglycemia episode, there is impairment in the patient's cognitive function—the higher-order brain processes, like thinking and memory. However, once the episode is over, it is not clear if there are long-term impairments. This picture is even more complex because insulin therapy itself may also directly affect cognitive function. Researchers are exploring these factors to better understand and prevent cognitive impairment in patients.

Building an Artificial Pancreas

Insulin therapy has improved tremendously over the past two decades, contributing to longer life and better quality of life for patients with type 1 diabetes. New forms of insulin, combined with new technologies for blood glucose measurement and portable “pumps” for insulin delivery, have enhanced the ability of patients to manage their blood glucose levels. Yet, current therapies to administer insulin are still inadequate substitutes for the body's own exquisite mechanisms for sensing and responding to insulin needs—mechanisms that are destroyed in type 1 diabetes. One major goal for research is to build an artificial pancreas. Ideally, this would be a mechanical insulin-delivery system that could monitor a patient's blood glucose levels continuously, and would respond by releasing appropriate amounts of insulin, as needed, in much the same way as a healthy pancreas. Such a system would spare patients from painful finger sticks to check glucose levels and from administering insulin injections or monitoring an insulin pump. It would also greatly decrease the risk of severe low blood glucose episodes while improving glucose control, thus reducing long-term complications. While development of an artificial pancreas will require time and careful testing, researchers are rapidly exploiting technologies and tools necessary for such a system, including the very new methods for continuously monitoring blood glucose levels.

Severe hypoglycemia is an acute and potentially deadly risk of insulin therapy. Thus, until it is possible to prevent, reverse, or cure type 1 diabetes in medical practice, a high-priority research goal remains the development of better means of controlling and preventing low blood glucose episodes in patients whose lives are dependent upon insulin therapy.



The Beauregard Family:

What It Is Like To Care for a Young Child with Type 1 Diabetes

The day after two-and-a-half-year-old Hannah Beauregard was diagnosed with type 1 diabetes, her parents, Doug and Mary, were being trained at their local hospital by a team of medical personnel on how to measure Hannah's blood sugar level. Blood sugar is measured in milligrams per deciliter of blood. Although people with diabetes have higher than normal blood sugar levels, they can also occasionally experience dangerous episodes of seriously low blood sugar. "At one point," Doug recalls, "I told the medical team that I must be doing something wrong because the monitor read 20 (milligrams per deciliter)." The proper target range for Hannah, if she hasn't eaten recently, is substantially higher. Before he knew what was happening, attending residents whisked Hannah from his arms and out of her hospital bed into what Doug can only describe as a "little emergency-type" room. "They shut the door and would not allow me in," he vividly recalls.

What Doug didn't know at the time was that Hannah was being administered a medication that acts like "instant sugar." Because Hannah's blood sugar levels had dropped precipitously, this treatment was necessary to prevent her little body from going into a coma. What Doug *did* quickly realize was that having a child with diabetes was going to alter life for the Beauregard family dramatically.

"You Are Not Alone"

Doug Beauregard is a third grade teacher and long-time soccer coach. His wife, Mary, is a registered nurse. Given their professions, one would think that they should know a thing or two about children and medical care—

and they do, a great deal. But having a young child with type 1 diabetes is often as difficult for them as it is for anyone else. "You are not alone," Doug wrote recently in an e-mail to another parent seeking advice on how to deal with a toddler with type 1 diabetes who was refusing to eat after taking her insulin. "We're facing the same problem with Hannah."

People with type 1 diabetes must carefully monitor their blood sugar levels throughout the day to determine when they need to eat, and administer insulin, either through injections or an insulin pump, to help their bodies use the sugar from carbohydrates in food. Both steps are also necessary to help keep blood sugar levels within a healthy target range. A constant challenge faced by people with type 1 diabetes is matching food intake, physical activity, and insulin doses in order to maintain healthy blood sugar levels. For example, although too little insulin leads to high blood sugar (hyperglycemia), administering too much insulin for the body's needs at a given time can cause blood sugar levels to fall too low (hypoglycemia). Dramatic rises and drops in blood sugar levels can have immediate and life-threatening consequences, and need to be avoided. Moreover, research has shown that carefully controlling blood sugar levels over the long term are crucial to help prevent serious complications of diabetes, such as diabetic eye, kidney, and nerve disease, and cardiovascular disease.

Controlling Sugar Levels Is a Constant Chess Match

Carefully controlling blood sugar levels, especially in a young child with type 1 diabetes, is no easy task. Just ask the Beauregards.

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According to Doug, since November 14, 2002, the day Hannah was diagnosed with type 1 diabetes, he and Mary have had few uninterrupted nights of sleep. “If Hannah snores, whimpers, cries, moves, or whatever, we wake up,” he says. “We can tell by the way she is sleeping if her blood sugar is low or high. If I think it is low, I will check her. If not, I try to comfort her.”

It has now been more than 3 years since Hannah was diagnosed. In that time, the Beauregards have been relatively successful at developing systems for keeping Hannah’s blood sugar levels within a normal range, especially at night, when levels tend to drop, a phenomenon called nocturnal hypoglycemia.

To compensate for sugar level drops over the night, Hannah’s parents try to put her to bed with a high enough blood sugar level so that she will wake up in the normal range. At least that’s the goal, but it’s a lot easier said than done. “It’s a constant chess match,” says Doug. “Her body makes a move; we make a counter move.”

For example, physical activities tend to decrease blood sugar levels. Hannah’s activities, like playing soccer, end about 7:00 p.m. To bring her sugar level up before she goes to bed, which is around 9:30 p.m., the Beauregards usually give Hannah a snack—a fruit snack, sometimes followed by a protein-rich food.

“There are many nights, however, when Hannah will wake up, get out of bed, and tell us she’s hungry,” says Mary. “I’ll check her levels and find that she’s in a low but not dangerous range. I’ll give her something to bring her level up a bit so she can safely get through the night. It’s as if her body is talking to her and telling her what she needs.”

But there are no hard and fast rules to this chess game. Hannah can go to bed with an acceptable blood sugar level on one night and wake up with a higher sugar level, but on another night, she might wake up with very low blood sugar, even if she started at the same point.

Then there are the real “Sugar Monster” nights when, according to Doug, there are no obvious reasons why

Hannah’s blood sugar will surge. Last Spring, for example, Hannah lay in her bed crying uncontrollably, with a very high blood sugar level. Doug gave her extra insulin to bring her level down, and 15 minutes later she stopped crying, was peaceful and sound asleep. “But we worried about her all night and wondered what her numbers would be like in the morning,” says Doug. In addition, the Beauregards run the battle of having to prick Hannah’s little fingers yet again to test her sugar levels—fingers that have already been pricked thousands of times. “It’s a question of whether we have faith in what we did,” says Doug. “Controlling Hannah’s sugar is really an art, not a science, and there are days I wish we didn’t have to go through all of this,” adds Doug.

When Hannah reminded her bear Rufus that it was time for his evening shot, she was really announcing to her parents that she was ready to have her own shot. The lesson: If Rufus can do it, Hannah can do it, too.

As a result of such diligence, Hannah’s hemoglobin A1c (HbA1c) tests have nearly always been good, between 6.9 and 7.1, which lowers Hannah’s risk for complications from type 1 diabetes. These tests are administered by her endocrinologist and are a good indicator of average blood sugar levels over a 3-month period.

It’s obvious that Doug and Mary love Hannah dearly. Doug, in particular, has made it his mission to tell everyone he can about Hannah and how special she is. “No one is responsible for Hannah’s having type 1 diabetes. It’s just part of her life, and we love her for who she is,” says Doug, who actively tries to help other parents whose children have this life-threatening disease.

In many ways, Doug is the consummate communicator. The very first night that Hannah was diagnosed, Doug was on the Internet searching for local support groups. Today, their family attends a support group near their hometown of Plainwell, Michigan. The group consists of families of children with type 1 diabetes who range

in age from 2 to 13 years old. Doug also frequently exchanges e-mails with people around the world, from Argentina to Newfoundland. “We are all seeking answers for our children,” says Doug. “We learn a lot through each other’s experiences and mistakes.”

What About All of Those Finger Pricks and Shots?

It is hard enough for adults with type 1 diabetes to take all of the steps necessary to take care of their disease. Therefore, the questions remain: How does a parent convince a small child with type 1 diabetes that enduring finger pricks to test blood sugar levels and shots to administer insulin, several times a day, is necessary in order to stay alive and healthy? How do parents feel about having to administer those finger pricks and shots?

To help the whole family adjust to Hannah’s new health needs, the Beauregards introduced Hannah to a friend—a fluffy brown teddy bear named Rufus. Rufus™, The Bear with Diabetes, was given to Hannah by the organization Childrenwithdiabetes.com. Within hours of their meeting, Rufus became Hannah’s fast friend. Rufus is designed so that he, too, needs to have his fingers “pricked” and to be given “shots.” It wasn’t long before Hannah was administering “shots” to Rufus. After finger pricks to test for sugar levels, both Hannah and Rufus would have their fingers wiped and a special Band-Aid applied. When Hannah reminded her bear Rufus that it was time for his evening shot, she was really announcing to her parents that she was ready to have her own shot. The lesson: If Rufus can do it, Hannah can do it, too.

Everyone in Hannah’s family—except 2-year-old Evan—knows how to care for her, including her 14-year-old brother, Ryan. “Ryan is really good with his little sister,” says Mary. “Yes, they fight and can drive us crazy at times, but Ryan and members of his soccer team know how to test Hannah’s blood sugar level,” adds Doug.

The good news is that the older Hannah gets, the more choices she can make for herself to help balance her diet, physical activities, and insulin injections so that she

can maintain healthy control of her blood sugar levels. As Hannah becomes more independent, it is becoming easier for her parents. Doug recounted an experience in which he encouraged Hannah in learning about the foods she needs to eat in order to obtain the proper amounts and balance of nutrients she requires at each meal, including carbohydrates. Says Doug, “At dinner the other day, Hannah said she was full. I told her that she needed to eat so she would get her carbs (carbohydrates). Hannah then asked, ‘Dad, does my bread have carbs?’ Yes, I told her. ‘How about my meat?’ No, I said. ‘I guess I will eat my bread then,’ she said.” Hannah recognized the need to have her carbohydrates to stay healthy. The Beauregards try to make Hannah feel in control of her diabetes as much as possible by giving her choices. “We also always have a fallback food just in case Hannah doesn’t want to eat what we have for dinner,” Mary adds.

As much as Doug and Mary sometimes feel they have things pretty much under control, “It’s not easy being a parent of a child with diabetes, and it never will be,” Doug says. The kindergarten Hannah attends, for example, was leery at first about having a student with Hannah’s disease, so the Beauregards had to educate the staff about diabetes and what to do if Hannah’s blood sugar level became too low or too high. “Part of the problem,” says Doug, “is that Hannah isn’t always

“Because Hannah is doing well, we want to get her story out to people. We feel we have something that we might be able to offer to other parents who are struggling with children who have this disease. It gives us strength.”

cooperative when her blood sugar level is low.” The family has shied away from day care. When Hannah was not in pre-school, Doug’s mother, Elizabeth—who is as well trained as Doug and Mary in how to care for Hannah—spent 2 or 3 days a week at the Beauregard home. Doug

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adds that when he is at work “my students know that if my cell phone rings, it’s something important.”

In short, life is a constant vigil.

Hannah is growing up to be an adorable little girl whose life will be in constant jeopardy until a cure is found for her type 1 diabetes. Until then, she will be required to take insulin every day of her life to survive.

“We’re not angry that Hannah has (type 1) diabetes,” says Doug. He and Mary just want to tell everyone they can about their little girl. “Because Hannah is doing well, we want to get her story out to people. We feel we have something that we might be able to offer to other parents who are struggling with children who have this disease. It gives us strength.”

“We need to be strong for every child with diabetes,” says Doug, “because without their parents, they won’t make it.”

Hope Through Research

To balance the long-term risks of developing complications associated with hyperglycemia with the short-term dangers of hypoglycemia, patients with type 1 diabetes and their families must perpetually face a chess match of measuring sugar levels and reacting to them with insulin or sugar. The opportunities identified in this chapter of the Strategic Plan outline multiple avenues of research that could help patients avoid hypoglycemia.

As a result of insulin therapy for type 1 diabetes, many patients experience low blood sugar at night during

sleep, a phenomenon known as nocturnal hypoglycemia. Sleep can be a particularly dangerous time because it inhibits the normal adrenaline responses that are usually triggered when blood sugar drops below a threshold level; the adrenaline and nervous system responses are needed to warn patients that they are in danger. Nearly half of all episodes of severe hypoglycemia occur during sleep and, in extreme cases, can lead to coma or seizures that can result in fatal cardiac arrhythmia (disturbed heartbeat).

Despite measuring blood sugar levels just before sleep, type 1 diabetes patients often find it difficult to predict the profile of blood sugar during the night. Research that explores the relationship among diet, behavior, insulin therapy, and the nocturnal sugar profile will make it easier to predict and prepare for changes in blood sugar during the night. For example, preliminary results from the Diabetes Research in Children Network (DirecNet) indicate that the timing of exercise during the day corresponds to the level to which blood sugar drops during the night. Relevant research that is under way or that is recommended in this Strategic Plan includes:

- ▶ Developing minimally invasive glucose sensors to facilitate continuous glucose monitoring, even while the patient is asleep;
- ▶ Mapping nocturnal glucose profiles to behaviors such as exercising before bed;
- ▶ Improving algorithms that allow patients to optimize long-lasting and short-acting insulin analogues;
- ▶ Closing the loop: developing an artificial pancreas that monitors blood sugar and automatically delivers insulin; and
- ▶ Determining the effects of hypoglycemia on long-term brain function.

