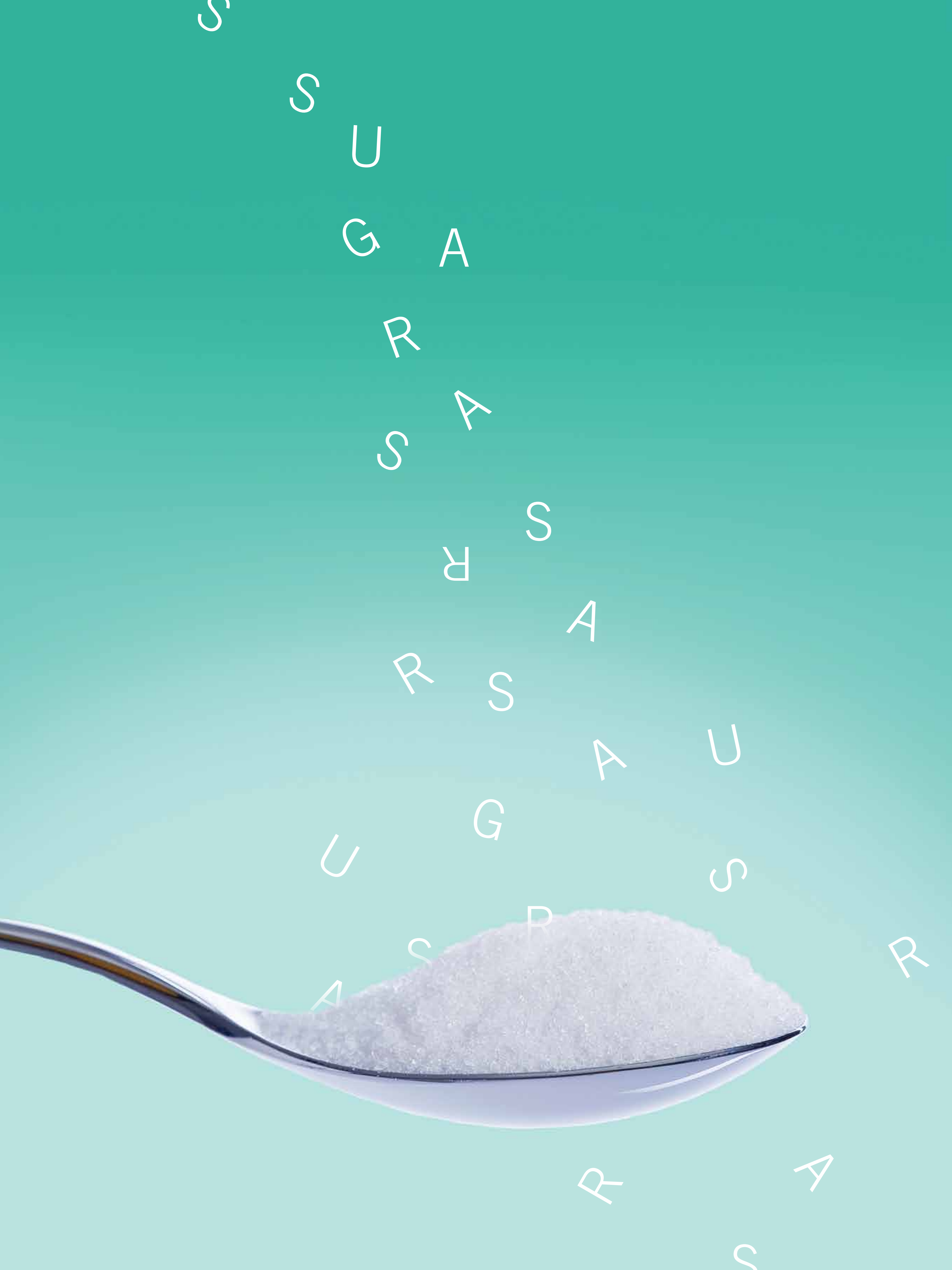

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Insulin is given to severely burned patients

to help regulate their blood sugar levels, but disastrous consequences can result when too little or too much is given. How, then, to determine that delicate, "just right" balance? BY ALISA KIM

A severe burn takes a devastating toll on the mind and body. Burn patients endure excruciating pain and undergo a lengthy recovery. Treating these injuries is complicated by the ensuing metabolic disturbances that can last up to one year. The stress response to a burn causes profound changes in the endocrine and immune systems, and an overall hypermetabolic state characterized by increased energy expenditure and body temperature and muscle wasting.

"The greatest metabolic need that you can have is burns," says Dr. Marc Jeschke, a scientist in the Trauma, Emergency & Critical Care Research Program at Sunnybrook Research Institute and director of the Ross Tilley Burn Centre at Sunnybrook Health Sciences Centre. "It beats any critical illness, any surgery, any trauma. Your metabolic demands are the equivalent of running marathon after marathon without any break."

Nutrition is a vital part of the treatment of burns, as the energy requirements of thermal injuries are immense. A patient with a burn covering 40% of his total body surface area can lose one-quarter of his weight by the third week after injury, even with substantial oral nutrition. Moreover, because protein is lost through the wounds, burn patients have increased caloric needs for healing. Burn injuries cause protein and muscle catabolism, whereby the body ravages its own protein stores for fuel, resulting in the loss of lean body mass. Without adequate nutrition these patients suffer from poor wound-healing, weight loss and weakened immunity.

Severe burns also damage the liver, preventing patients from properly metabolizing fats. Thus, carbohydrates, which are broken down into glucose, provide burn patients with most of their caloric needs. Due to the stress of frequent interventions and high-carbohydrate feeds, however, these patients are prone to hyperglycemia, or high blood sugar.

Hyperglycemia, which is common in intensive care unit (ICU) patients—even among those who do not have diabetes—is a much-studied phenomenon. It is associated with higher rates of infection, organ failure and even death. Burn patients with high blood sugar experience a prolonged hypermetabolic state, putting them at risk of infection and muscle wasting. When blood sugar levels rise above 160 milligrams (mg) per decilitre of blood, there is protein glycosylation. This occurs when a sugar molecule binds to a protein in an uncontrolled way and the protein is altered. Protein glycosylation can lead to multi-organ failure.

The paradigm of glycemic control in critical care medicine was introduced in 2001 through a practice-changing study published in the *New England Journal of Medicine* by researchers from the Catholic University of Leuven. Dr. Greet Van den Berghe and colleagues showed insulin given to postoperative surgical patients to keep glucose levels between 80 and 110 mg per decilitre of blood decreased rates of mortality and the incidence of infection, sepsis and organ failure.

Soon after the study's publication, critical care units worldwide began adopting protocols to keep patients within this tightly controlled range. Within a few years, ICUs and trauma centres reported that intensive insulin therapy targeting glucose levels of 80 to 110 mg per decilitre posed risks of hypoglycemia (low blood sugar), which is just as dangerous as hyperglycemia, if not more so. In the decade following the release of the Leuven study, glycemic control in the care of critically ill patients has been the topic of much controversy.

Not as well documented, hypoglycemia is thought to be lethal for critically ill patients. Burn patients are at risk of low blood sugar as nutrition, which is delivered via a feeding tube, is interrupted due to operations, dressing changes and daily showers to keep wounds clean. Severe hypoglycemia (blood sugar levels under 40 mg per decilitre) is believed to cause brain damage, immune impairment and organ failure, says Jeschke, who is studying the outcomes associated with it in collaboration with researchers from Texas and Germany.

"We know glucose is the main energy source for the body, but too much is not good and too little is not good," says Jeschke, who is responsible for the care of about 250 burn patients annually, and sees firsthand the dangers of hyperglycemia and hypoglycemia in burn patients.

In 2009, researchers from Australia, New Zealand and Canada (including two from Sunnybrook Research Institute) published a study titled "Normoglycemia in Intensive Care Evaluation–Survival Using Glucose

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DR. MARC JESCHKE

Algorithm Regulation (NICE–SUGAR). They conducted a multicentre trial with more than 6,000 critically ill patients to compare the effects of tight glucose control to conventional glucose control therapy (keeping blood sugar levels at or less than 180 mg per decilitre). After 90 days, there were 829 deaths among patients who received insulin to keep glucose levels within the range from the Leuven study, compared with 751 deaths among those who received conventional therapy.

The conflicting evidence from the scientific literature raises the question: in critically ill patients, how much glucose is too much?

The answer, it turns out, may depend on the patients themselves. Research suggests postoperative surgery patients benefit from tight glucose control, while critically ill medical patients, including burn patients, do not respond as well to it. The trauma of burns differs in severity and length from that of other critically ill patients; burn patients have longer hospital stays, more complications and are more likely to die compared with general ICU patients. The NICE-SUGAR study showed the only patients who benefited from intensive insulin therapy were trauma patients and those who needed corticosteroids to treat septic shock and other serious conditions.

Given that burns are an extreme form of trauma, and a high degree of sickness and death is associated with hyperglycemia in burn patients, glycemic control makes sense—but how tight should this control be?

Finding no answers to this question in the literature, Jeschke, who is also a professor of surgery at the University of Toronto, entered the debate. "We took all this data that are saying different things, and asked what is a good range?" he says.

Specifically, his aim was to determine which glucose levels were associated with improved outcomes in burn patients. The study involved 208 pediatric patients with burns to over 30% of their total body surface area. Based on 6:00 a.m. glucose level measurements, patients were divided into groups based on good glucose control and poor glucose control. The former were those patients whose glucose levels were 130 mg per decilitre or less for at least 75% of their hospital stay; the latter were those whose glucose levels were higher than 130 mg per decilitre.

Jeschke found that patients with good glucose control had a lower incidence of infection, sepsis and death compared with patients with poor glucose control. He also found that patients with good glucose control had milder inflammatory and hypermetabolic responses. "We found that 130 mg per decilitre is one of the ranges burn patients should be in. This is in line with critical care guidelines and sepsis guidelines, which are in the 130 to 150 [mg per decilitre] range," says Jeschke.

The results of his inquiry were published in the *Annals of Surgery* in 2010.

"Our data demonstrate that the ideal glucose target is around 130 to 140 mg per decilitre, and that the glucose curve has a U-form shape, meaning that very low glucose levels are as detrimental as very high glucose levels," says Jeschke.

With no other published research on target glucose ranges to guide clinicians in the treatment of burns, Jeschke's work is all the more valuable.

"Prior to Marc's research, everybody was trying to get to 80 to 110 [mg of glucose per decilitre]," says Dr. Steven Wolf, vice-chair of research and the burn section chief at the University of Texas Southwestern Medical Center. "There was a lot of resistance, but the only data we had was [the] Van den Berghe [study]. People were trying to do that and noticing that we're seeing more hypoglycemia than we normally do. That's when backing off of the range seemed to be a prudent goal, and that's what Marc showed."

Wolf, who is editor of the journal *Burns*, says that he and his colleagues at other burn centres are using more moderate glucose ranges as therapeutic targets and that this practice is guided by empirical evidence. "Other than a few reports—one of them being Marc's—people aren't really talking too much about it; they're just kind of doing it," he says. "The question is: is not-so-tight [glucose] control as effective? Marc is showing that maybe it is. We can get less risk and the same benefit, which is the optimal solution."

Jeschke is using the findings from this research in a clinical trial he is leading at Sunnybrook. He will study the effects of glucose levels between 130 to 140 mg per decilitre in severely burned patients to see whether improved outcomes through glycemic control are due to insulin-specific responses.

As the only study thus far to zero in on an optimal glucose range for burn patients, Jeschke's research has attracted a lot of attention. In a letter to the editor of the *Annals of Surgery*, Drs. Hanazaki, Munekage and Okabayashi from the department of surgery at Kochi Medical School in Japan write: "We believe this is a crucial article in our understanding of the efficacy of tight glycemic control for critical surgical patients." Others apparently think so, too: "Most burn centres and critical care units are now using a 110 to 130 mg per decilitre range," says Jeschke.

But what excites him most about the study's findings is the potential to do better by patients. "We finally have an idea what glucose range is on one hand beneficial for survival, but on the other hand safe for burn patients. By identifying the exact range, patient care is safer."

"The greatest metabolic need that you can have is burns," says Dr. Marc Jeschke.

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