

## Advances in Insulin Injection Research Influences Patient Adherence

Ronnie Aronson, MD,<sup>1</sup> Timothy Bailey, MD,<sup>2</sup> Laurence Hirsch, MD<sup>3</sup> and Rita Saltiel-Berzin, RN, MPH, CDE<sup>3</sup>

1. Executive Director, LMC Endocrinology Centres, Toronto, Ontario, Canada; 2. Director, AMCR Institute, Inc., Escondido, California, US;  
3. BD (Becton Dickinson and Company), Franklin Lakes, New Jersey, US

### Abstract

Insulin formulations and injection devices have improved dramatically since the first insulin injection was given in 1922. Adherence to insulin therapy, however, is estimated at 62–64 % despite research indicating that good glycemic control improves patient outcomes. The challenge is to improve the rates of adherence and to intensify or progress insulin therapy as needed. Changes in insulin delivery devices, especially innovations in needle technology in combination with education and support, have the potential to improve the comfort of insulin injections and encourage patients to adhere to their insulin regimens.

### Keywords

Insulin pen needles, adherence to insulin therapy, psychological insulin resistance, skin thickness

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**Correspondence:** Ronnie Aronson, MD, LMC Diabetes & Endocrinology, Suite 106, 1929 Bayview Avenue, Toronto, ON, Canada M4G 3E8. E: ronnie.aronson@lmc.ca

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The emergence of new formulations of insulin and injectable medications has made insulin therapy safer and more effective. Evolution has stimulated innovations in insulin delivery systems that, in turn, may positively affect patient comfort and adherence to insulin therapy. This article will review the progress made in understanding skin and subcutaneous (SC) fat thickness at injection sites, its implications for the design of an optimal needle for injecting insulin, and the potential impact on patient adherence.

### Background

The first insulin injection was given in 1922 to Leonard Thompson, a 14-year-old boy in Canada, who was near death from type 1 diabetes. The injection was given with a glass hypodermic syringe and bare steel needle. Insulin was heralded as a lifesaving drug and its founders were awarded the Nobel Prize, in 1923.<sup>1</sup> The first insulin syringe specifically manufactured for insulin therapy became available in 1924 and included a 25-gauge (G) needle. Syringes and needles were boiled to sterilize them before use. Needles were sharpened with a whetstone, which most people associate with the sharpening of knives. This process continued until 1961, when the first disposable plastic insulin syringe was introduced, the forerunner of today's syringe with an integrated or staked needle.<sup>2</sup> Insulin pen use began in the 1980s as an alternative to insulin vials and syringes. Shaped like a fountain pen, they contain a cartridge of insulin and require a dual-ended pen needle, attached separately before the injection. Patients simply dial a dose of insulin and push a button to

deliver the desired amount. This development allowed insulin injections to be given in a more convenient and simple manner.

To provide a historical perspective to the evolution of changes in needle length and gauge (diameter), one only has to compare the sizes of insulin needles over the years (see *Figure 1*). In 1985, insulin was given in a syringe with a 27G, 16 mm needle. Today, insulin syringes are available with needles as short and thin as 6 mm, 31G, or via insulin pen with needles as small as 4 mm, 32G. A 32G needle has an external diameter of approximately 0.23–0.24 mm, or 0.009 inch (ISO Standard 9626)—not much different from a human eyelash.

Studies have consistently shown that glycemic control is equivalent, regardless of needle size used, and that patients preferred the shorter, finer-gauge (smaller diameter) needles, reporting less pain, and generally no difference in backflow or insulin leakage from the skin.<sup>3–11</sup> Recently, needle tip bevels have been ground to become even sharper and flatter, penetrating the skin with less force, leading to a more comfortable injection.<sup>12</sup> Recently, the cannula wall has been made thinner (while preserving the external dimensions), making a larger inner diameter of the needle and requiring less force to push the button on the pen that delivers insulin (and/or less time to dispense the dose).<sup>13</sup> Although not visible to the user, these technological advances make injections more comfortable and easier to administer. They have helped patients

to meet the demands of flexible therapy in a modern lifestyle requiring convenience, flexibility, and discreteness.

## Psychological Insulin Resistance

Despite these advances, patients have remained reluctant to begin therapy, often called 'psychological insulin resistance' (PIR).<sup>14–17</sup> When insulin is initiated, adherence of patients with type 2 diabetes has been estimated at only 62–64 %. Adherence has been found to decrease with polytherapy and multiple doses of insulin. Even among younger patients with type 1 diabetes, prescriptions are filled for only one-third of the insulin dose prescribed.<sup>18</sup> Patients may intentionally miss a dose of insulin because it is perceived to interfere with lifestyle and/or cause embarrassment outside of the home setting.<sup>19</sup>

Insulin therapy is often viewed by the patient as a consequence of an unhealthy lifestyle, lack of exercise, and poor food choices. It is regarded as a personal failure. Patients perceive themselves as 'sicker.' In one study, 35 % of patients believed that insulin therapy would result in blindness, renal failure, amputations, heart attacks, strokes, or early death.<sup>15,16,20,21</sup> Adding to these barriers are low self-efficacy relative to properly administering the injection, fear of hypoglycemia, perceived negative impacts on social life and employment, and inadequate health literacy.<sup>14,17</sup> Patients also report receiving incomplete explanations of the risks for and benefits of insulin therapy.<sup>15</sup> Often, the result is years of inadequate glycemic control.<sup>22</sup> Adherence may therefore be viewed as a result of multiple factors, poor comprehension of the treatment regimen, its benefits, costs, and complexity.

When patients understand that insulin administration has a positive impact, rates of adherence improve. Patients on polytherapy regimens were found to be 10–20 % less adherent than those on monotherapy.<sup>17</sup> In addition, intentional omission of injections occurs in approximately 20 % of people surveyed and may be related to convenience and lifestyle matters.<sup>19</sup>

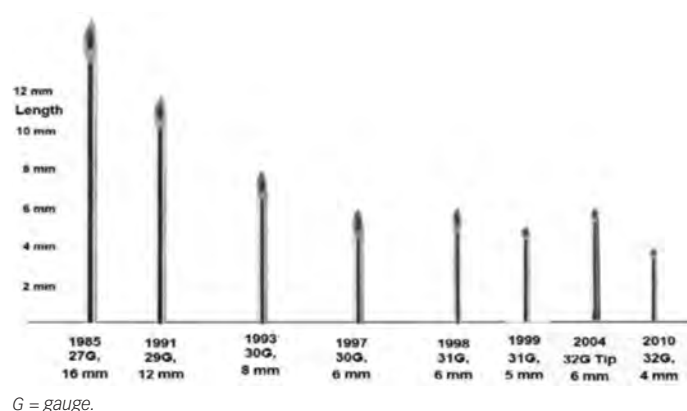
Strategies to address these factors include verifying patient's recall and comprehension of the treatment regimen and simplifying the regimen to reduce the burden of costs and tasks. Initially this requires engaging patients in shared decision-making and comparing the benefits of treatment with potential adverse events.<sup>21</sup> Counseling patients in integrating the regimen into their daily routine, the management of adverse events, and simplifying the regimen to include fewer medications or less-frequent dosing has resulted in improved adherence rates.<sup>17,19,21</sup> The use of an insulin pen and pen needle also serves to make the injection process more convenient and less burdensome.

Physicians also demonstrate PIR. In a web-based survey administered to 600 physicians across six countries, nearly 40 % of primary care physicians and 30 % of specialists found adding bolus insulin therapy difficult and indicated they needed more support staff and resources to assist them. About half reported they lacked experience with the newer insulin analogs, and felt that the education of patients was too time-consuming. Almost 40 % believed that patients could not cope with multiple insulin doses.<sup>15,17,18</sup>

## Pain

Pain is a barrier to both initiating and intensifying insulin regimens. Even among patients familiar with insulin therapy, 38 % of patients still reported

**Figure 1: Changes in Insulin Needle Length and Gauge—1985–2010**



that injections were painful.<sup>17,21</sup> Pain from injections has been attributed to three factors: needle length, diameter, and the individual's perception.

## Needle Length

An effective insulin injection delivers insulin in the SC adipose tissue, avoiding the muscle fascia. Intramuscular injections are more painful. In a recent study, the mean skin thickness by high-frequency ultrasound was found to be ~2.0–2.5 mm at the four common injection sites, with few measurements above 3.0 mm.<sup>23</sup>

## Needle Diameter (Gauge)

Patients historically have reported frequent painful injections with lower-gauge (larger-diameter) needles. Many studies have now consistently demonstrated less pain associated with progressively higher-gauge needles, including laboratory tests controlling for insertion speed, force, and angle of skin penetration.<sup>3–11,24</sup>

## Patient Perception

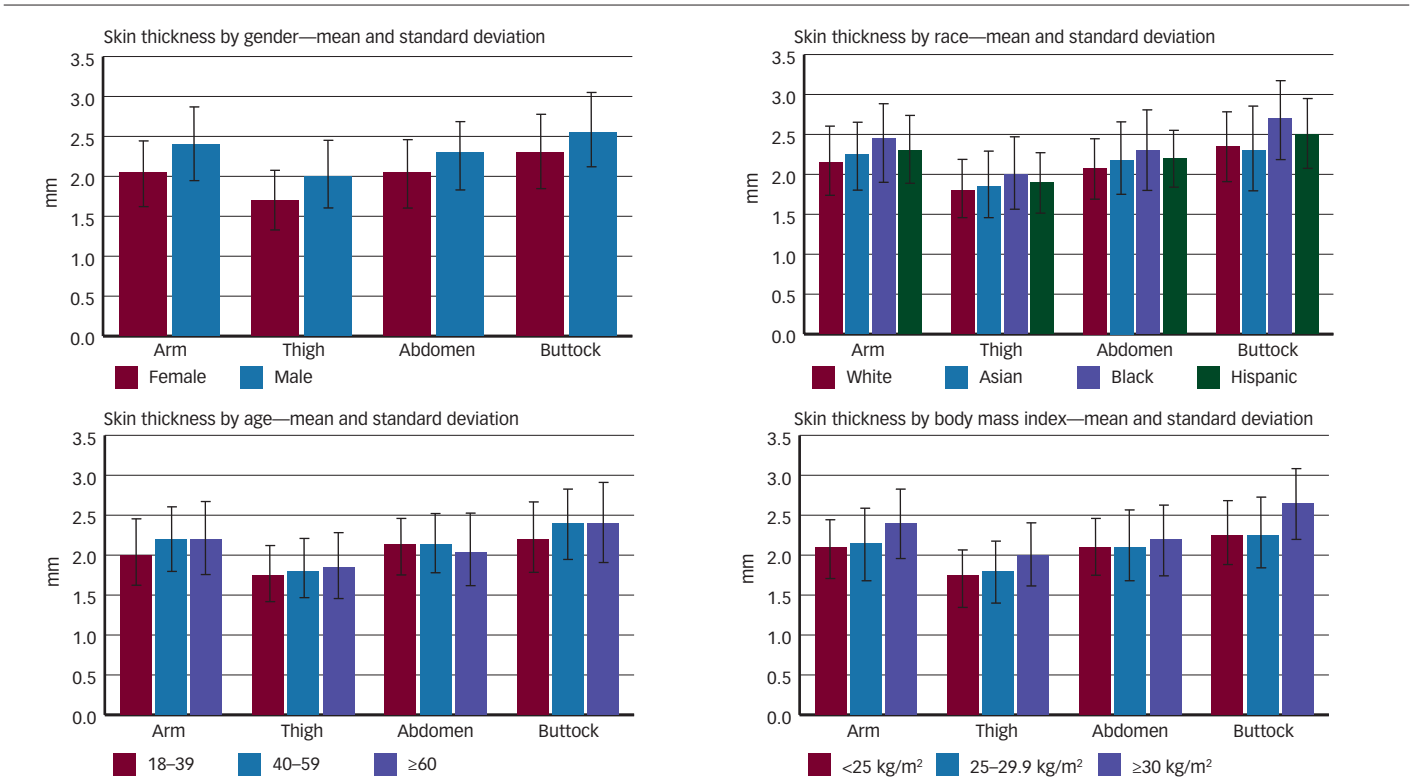
Pain has been identified as a barrier to patient adherence and has often been related to the visual appearance of the needle. Pain is also related to the injection experience: those who received injection training and were insulin experienced placed less importance on the route of administration than insulin-naïve patients.<sup>17</sup> Research has shown that shorter, finer-gauge needles are preferred by patients and may influence adherence.<sup>3–11</sup> The development of shorter-length needles for injection is supported by a recent study of skin thickness in people with diabetes, noted previously.<sup>23</sup>

## Injection Site Anatomy—Skin Thickness

To ensure an effective injection, the needle must penetrate the skin and deliver the insulin into the SC adipose tissue avoiding the muscle fascia. This allows the absorption of insulin at a consistent rate, depending on its formulation. There is a belief among many healthcare providers that insulin should be deposited deep into the SC space. Frid et al. found that there was no difference in absorption whether insulin was delivered deep or superficially into the SC space.<sup>25</sup>

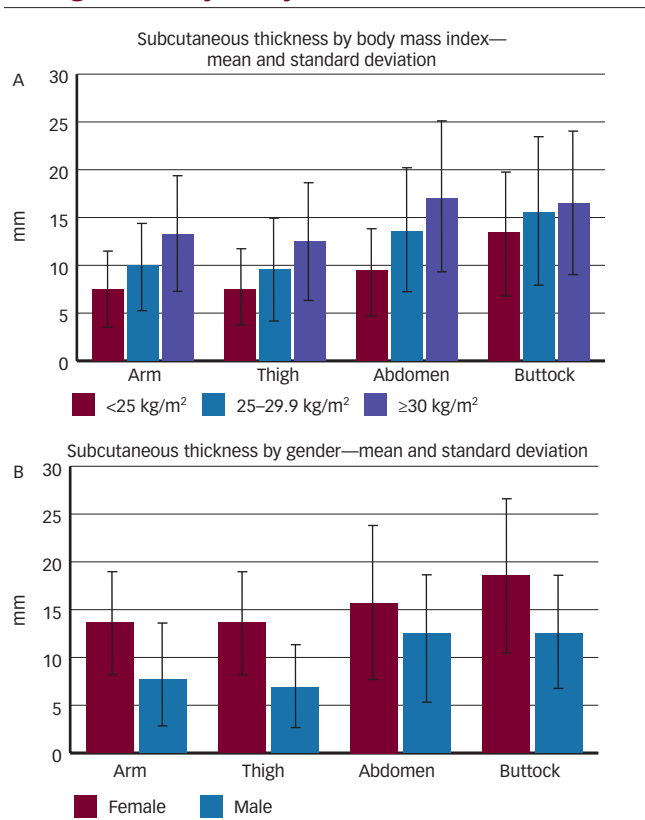
To better understand the nature of the skin and the SC tissue that the needle must penetrate, Gibney et al. examined the thickness of skin and SC fat at injection sites of patients with diabetes using high-frequency

Figure 2: Summary of Skin Thickness Results by Body Mass Index, Age, Race, and Gender



Source: adapted from Gibney et al.<sup>23</sup>

Figure 3: Subcutaneous Fat Thickness Categorized by Body Mass Index and Gender



Source: Adapted from Gibney et al.<sup>23</sup>

ultrasound. Patients came from diverse ethnic backgrounds, were evenly matched by gender, included a mix of type 1 and 2 patients, and ranged in age from 18–85 years with body mass index (BMI) from 19.6 to 64.5 kg/m<sup>2</sup>.<sup>23</sup> Figure 2 shows the skin thickness values according to body site. There is little variation between body sites and very little variation related to common demographic factors. The thickness is similar by age, gender, race, and BMI at the four injection sites. Overall, the skin at the thigh is the thinnest (mean 1.9 mm) and thickest at the buttock (mean 2.4 mm), a difference of <0.6 mm. The participants with BMI >30 kg/m<sup>2</sup> had slightly higher skin thickness; overall, there were few readings exceeding 3.0–3.1 mm. The authors concluded that shorter needles, even 4 mm, are appropriate choices for injecting insulin or other medication into the SC space, including in obese subjects.

Additional analyses indicated body site, gender, BMI, and race are statistically significant factors for skin thickness, but effects are small and of no clinical relevance. BMI differences of 10 kg/m<sup>2</sup> account for only 0.2 mm skin thickness variation, i.e. the skin thickness difference between patients with BMI of 25 versus 35 kg/m<sup>2</sup> was only 0.2 mm.

Subcutaneous Fat Thickness

As expected, with increasing BMI there is a significant increase in SC fat (see Figure 3A). Mean SC thickness for the entire population was: arm 10.8 mm, thigh 10.4 mm, abdomen 13.9 mm, and buttocks 15.4 mm.

Figure 3B shows that SC fat thickness in females was 5.1 mm greater than in males, related to sexual maturation through puberty.<sup>26</sup> In general, differences of 10 kg/m<sup>2</sup> account for a difference of 4 mm of SC thickness, which is clinically important.

## Implications for Clinicians

These findings support the use of shorter needles for nearly all patients regardless of BMI. Based on these results, it is estimated that the perpendicular insertion of 4 mm needles will deliver insulin into the SC space >99.5 % of the time, without entering the intradermal or intramuscular (IM) space.<sup>23,27</sup> The danger of inadvertent IM injection is that insulin action may be potentiated with large effects of exercise of the injected tissue, resulting in unpredictably faster absorption and earlier onset of peak activity, thus increasing the risk for hypoglycemia and glucose variability that may not be easily recognized.<sup>28</sup> In addition IM injections are often reported as painful.

Based on the measurements obtained through this study of skin and SC adipose thickness, estimates of the risk for IM injections without a skin pinch were calculated (see *Table 1*).<sup>27</sup>

These risk estimates do not represent actual risks at each injection site, rather, the data were pooled across the four common insulin injection sites. These estimates clearly show the risk for an IM injection increases directly as the length of the needle increases: compare a 4 mm needle with an estimated 0.4 % risk for IM injection to a 12.7 mm needle with a 45.0 % risk. The risks at each injection site have been calculated—there are significant differences between the abdomen and thigh (the latter roughly two to four times higher) which are the two most commonly used injection sites.<sup>23,27,29</sup>

These findings are confirmed by magnetic resonance imaging (MRI) images demonstrating the clinical relevance of these data for injection techniques (see *Figure 4*). Injections of 40 uL (equal to 4 ‘units’ of U-100 insulin) of sterile saline were made into the thigh of a 56-year-old male with a BMI of 25.2 kg/m<sup>2</sup>. The injections were given using a ‘no-pinch’ technique with a 4, 5, 6, and 8 mm pen needle. *Figure 4* illustrates that a 90° ‘no-pinch’ up technique can be safely used with a 4 mm or 5 mm pen needle to deliver insulin into the desired SC space. However, when using a 6 mm or 8 mm needle a ‘pinch-up’ technique should be used to avoid an IM injection.

## The 4 mm Pen Needle

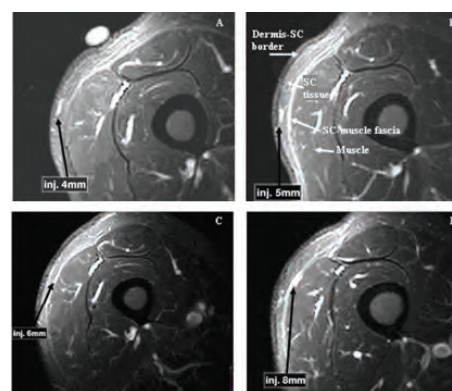
The skin and SC thickness study provided the evidence for the development of the 4 mm pen needle. In a randomized crossover controlled study, the 4 mm pen needle was compared with the 5 mm and 8 mm, 31G pen needles.<sup>3</sup> Results indicated equivalent glycemic control without increased insulin leakage from the skin. Additional findings were greater patient preference, acceptability, and reports of less pain with the 4 mm pen needle using a visual analog scale. There were similar rates of reported hyper- and hypoglycemia when using the different length needles. This finding is consistent with a number of other studies comparing pen needles of differing dimensions—shorter needles have been demonstrated to have equivalent glucose control to longer needles (including 8 and 12.7 mm), and are generally preferred by patients and rated as more preferable.<sup>4–8,10,11</sup>

An additional innovation to pen needles was the development of an extra thin wall (XTW) cannula. This needle has the same outer diameter, but the cannula wall is ‘thinned’ so that the inner diameter is >30 % larger. In quantitative testing (bench testing) the XTW needle improved the flow of insulin by 108 % to 149 % and reduced the time required to deliver the medication by 52 % to 60 % compared with 31G and 32G comparable

**Table 1: Risk Estimates of an Intramuscular Injection Based on Pen Needle Length**

Pen Needle Length	Risk for Intramuscular Injection
4 mm	0.4 %
5 mm	1.8 %
6 mm	5.7 %
8 mm	15.3 %
12.7 mm	45.0 %

**Figure 4: Magnetic Resonance Imaging Depicting the Results of Injections of 40 uL\* of Sterile Saline into the Thigh of a 56-year-old Male with a Body Mass Index of 25.2 kg/m<sup>2</sup>**



\*Equal to 4 ‘units’ of U-100 insulin. A: 4 mm needle, saline is injected in the subcutaneous space under the skin but above the muscle fascia. B: 5 mm needle and a similar result as A. C: 6 mm needle. The saline can be seen at the level of the muscle fascia. D: 8 mm needle deposited the saline intramuscularly. Source: Magnetic resonance images provided by Drs Anders Frid and Björn Lindén, 2010. Reprinted with permission from Current Medical Research and Opinion.<sup>23</sup>

thin-wall needles. The thumb force required to depress the button on the pen using the XTW needle was also reduced by 47 % to 62 % versus the thin-wall pen needles (all,  $p < 0.05$ ).<sup>13,30</sup>

In a crossover clinical study in the home setting, patients used the XTW needle with insulin pens from Novo Nordisk, Lilly, and Sanofi-Aventis. Subjects preferred the XTW pen needles compared with their usual needles overall (68.2 % versus 11.6 %). They also perceived less thumb force required to press the pen button (60.6 % versus 7.1 %), shorter time to inject (48.5 % versus 4.5 %), greater confidence that the full dose was delivered (51.5 % versus 9.1 %), less pain (48.5 % versus 4.5 %), improved insertion ease (63.6 % versus 6.1 %), and greater convenience (36.4 % versus 4 %). All results were statistically significant ( $p < 0.001$ ). Subjects indicated greater confidence in completing their injections and significantly fewer events of leakage, bruising, and bleeding at the injection site compared with their usual pen needles.<sup>13,29</sup> The 4 mm XTW Pen Needle has received the American Arthritis Foundation Ease-of-Use Commendation, for ease of use.<sup>31</sup>

## Leakage

In contrast to rigid-barrel syringes, pens do not deliver insulin immediately upon pressing a button. Hydraulic pressure is produced in the insulin cartridge by movement of the flexible septa at either end of the drug

container, resulting in a delay in the administration of insulin. This delay cannot be seen by the patient and may contribute to leakage that is sometimes seen both from the pen needle (continued flow of insulin) and/or at the site following an injection. Patients who withdraw the pen needle prematurely are more likely to see leakage. The concern is that insulin leakage may be enough to contribute to glycemic variability. Many healthcare providers are under the impression that leakage increases with shorter needles, especially in obese patients. However, studies have indicated that leakage is related primarily to dose volume, and not to needle length. In quantitative testing (bench), regardless of needle length, amounts of leakage varied from less than one unit to <1 % of the total dosage.<sup>32</sup> A second study measured leakage following injection and found the amount of leakage equivalent to a fraction of a unit.<sup>33</sup> Pen needle lengths from 4.0 to 12.7 mm may be used regardless of insulin dose injected. Short needles are safe and sufficient for injections in SC tissue for most patients, including those who are obese, without an increase of leakage.<sup>3,4,6,10,13,27</sup> To minimize leakage, after pushing the thumb button in completely, patients should count slowly to 10 before withdrawing the needle. Counting past 10 may be necessary for high doses. Additional time should be added to each injection until no leakage is observed.<sup>34</sup>

The 4 mm pen needle allows a 90° insertion without pinching up the skin unless the patient is extremely thin, or less than 6 years old.<sup>35</sup> Since pinching is not required, a one-handed method of insulin injection is possible. Patients who have difficulty reaching the back of their arms and the buttocks area were previously limited to giving insulin to their

abdomen and thigh. The use of the 4 mm needle allows access to those more-difficult-to-reach spots and allows for easier site rotation. This is important in light of a recent Spanish study which found nearly two-thirds of patients examined had lipohypertrophy.<sup>36</sup> The prevalence of LH was strongly associated with poor injection site rotation practices. Less painful injections that are easier to administer at more body sites may help reduce the development of LH.

## Conclusions

Advances in insulin therapy and needle technology have led to greater patient comfort and convenience, with dramatic improvements since that first injection in 1922. The research in patient adherence indicates that technology has a role in helping patients follow their insulin regimen. Shorter, thinner needles are preferred for many reasons: they are more comfortable, easier to use, and, in combination with insulin pens or syringes, improve patient convenience. Convenience and improved comfort may encourage people to adhere to their insulin regimen. These devices in combination with education and support may have an impact on patient adherence. Gherman et al. found that people who are more adherent to their insulin therapy had high levels of self-efficacy or confidence in their ability to follow their regimen, believed the outcomes would be positive and had a positive relationship with their healthcare provider.<sup>37</sup> Patients' sense of self-efficacy can improve with education and support. The use of newer and improved insulin delivery devices should help people with diabetes understand that they can fit insulin injections into their lifestyle. ■

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