*Review Article*

# Needle Technology for Insulin Administration: A Century of Innovation

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## Abstract

Innovations in syringe and pen needle (PN) technology over the last 100 years have led to important advances in insulin delivery for people with diabetes, paralleling the strides made in developing recombinant DNA human insulin and insulin analogs with varying onset and duration of action. In this review, the history of advances in insulin delivery is described, focusing on progress in syringe, needle, and PN technologies. The early glass and metal syringes that required sterilization by boiling have been replaced by disposable, single-use syringes or pens with clear labeling for precise insulin dosing. The early needles ranging in length from 19 to 26 mm that required manual sharpening against a whetstone have been replaced by syringe needles of 6 mm and PNs of 4 mm in length as slender as 34 gauge. Imaging studies using ultrasound and computed tomography measured the thickness of skin and subcutaneous tissue layers to show feasibility of targeted insulin administration with shorter needles. These developments, coupled with innovations in needle/PN wall and tip structure, have led to improved injection experience for people with diabetes. It is also important to acknowledge the role of injection technique education, together with these advances in injection technology, for improving clinical outcomes and patient satisfaction. With continued projected growth of diabetes prevalence, particularly in developing countries where expensive and complex insulin delivery systems may not be practical, insulin syringes and pens will continue to serve as reliable and cost-effective means of insulin delivery for people with diabetes.

## Keywords

insulin administration, insulin therapy, needle length, insulin pen, subcutaneous, syringe

## Introduction

The century since insulin was discovered in 1921 has witnessed tremendous change and improvements in insulin therapy for people with diabetes mellitus. Considerable advances have been made in isolating and purifying insulin and in manufacturing recombinant DNA human insulin and insulin analogs with varying onset and duration of action to better match physiological insulin requirements.

Methods of insulin delivery likewise have improved greatly over the past 100 years. Improvements in syringe and needle technology have led to other innovations, including insulin pens, which have now become "smart" (eg, with bolus calculator) and connected (for remote monitoring). Insulin pumps, connected with systems for continuous glucose monitoring (CGM) have evolved into automated insulin delivery systems with algorithms that control them. Many of the insulin delivery technologies have evolved from simple syringes, and to this day, the foundations of insulin delivery are based on delivering insulin from a "chamber" via piston/piston-like mechanism to the subcutaneous (SC) tissue for absorption into the bloodstream.

The aim of this review is to describe the history of advances in insulin delivery, with focus on progress in syringe, needle, and pen needle (PN) technologies. In addition, the benefits of

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these advances for people with diabetes are discussed, not only in terms of glycemic control, but also with regard to improved comfort and ease of administration.

## History of Syringes and Pens Used for Subcutaneous Insulin Administration

The first syringes used for parenteral administration of insulin were made of metal and glass.[1] These reusable syringes were costly, cumbersome to use, and prone to leakage, slipping, and breaking. Both syringes and needles required regular sterilization by boiling them in water. In 1924, Becton, Dickinson, and Company (BD, Franklin Lakes, NJ) introduced the first specialized insulin syringe, which was shortly followed by the Novo syringe from Novo Nordisk (Bagsværd, Denmark) in 1925.[2] In 1930, Fairleigh S. Dickinson obtained a patent for a Luer lock fitting for hypodermic syringes, an invention that contributed to reducing syringe disengagement during injection and led to the development of disposable Luer lock syringes.[3,4]

The first disposable glass syringe, the Hypak™ syringe from BD, became available in 1954, followed the next year by the first all-plastic syringe (Monoject™, Roehr Products Inc., Waterbury, Connecticut).[1] Developments in the 1960s included BD's 1-mL Luer-Lock insulin syringe available with either a detachable or permanently attached needle and the widespread availability of disposable plastic syringes.[1,2] New technologies had to be developed to enable smooth functioning of these plastic syringes, such as adding silicon oil to reduce friction between the plunger and the wall of the syringe.

The widespread production of plastic syringes by several manufacturers introduced new concepts regarding insulin syringe use: disposability, discretion, and affordability. Moreover, safety improved as the syringe barrels were labeled to match the units of insulin dispensed with the standardization to U-100 syringes.[1,2]

The availability of disposable syringes has improved the quality of life of people with diabetes; however, their availability has also contributed to substantial increases in the volume of medical waste and sharps hazards for sanitation workers, dual challenges for communities around the globe.[5]

The subsequent introduction of insulin pens offered patients more flexibility and an accurate and discrete option for insulin delivery.[2] The first reusable insulin pen, the NovoPen, was launched by Novo Nordisk in 1985.[2] Uptake of these devices was very rapid in the European Union and Japan but was slow in the United States, where cost and lack of insurance reimbursement were major barriers to their adoption.[1,6]

## History of Innovations in Needle Technology

At the inception of SC insulin therapy, the primary focus of needle technology revolved around ensuring delivery of insulin into the SC compartment, whereby the needle has to penetrate the skin and the needle tip accesses the SC adipose tissue, while avoiding the muscle and muscle fascia. It should be acknowledged that diabetes was the first condition for which patients were given the responsibility of regularly self-injecting a drug, a highly potent drug, and not all physicians at the time were aligned with this therapeutic plan.

With time, as needles became more sophisticated, the focus of developments in needle technology broadened to include the patient perspective—minimizing injection pain, maximizing ease of use—as well as minimizing the risk of intramuscular (IM) injection. New assessments of patient-reported outcomes (PROs) included measures of preference, required thumb force, ease of pen use, and the frequency and intensity of pain with insulin administration.[7,8] Innovations that spurred reductions in needle length and diameter (gauge), together with changes in needle tip and needle hub geometry, were accomplished alongside breakthroughs in understanding of the anatomy and physiology of skin and SC tissue.[9]

### *Needle Length and Gauge*

*Needle length and injection site.* The first needles used to inject insulin were the same as those used for general medical purposes and were much longer and larger in diameter as compared with today's syringe needles and PNs. These early needles ranged in length from 19 to 26 mm and were manually sharpened for repeated use against a whetstone by the user.[10,11] Their length and design could evoke anxiety and tension in people with diabetes, especially children. Looking from today's perspective we now understand that these early needles posed substantial risks for IM injections by people self-injecting insulin.[9] In 1985, when the first widely used insulin pen was introduced by Novo Nordisk, the PN length most commonly available was still 16 mm (Figure 1).[11] Today, by comparison, the needles preattached to disposable U-100 insulin syringes are as small in diameter as 31 gauge (G) and as short as 6 mm, while PNs can be as thin and short as 34G x 3.5-4 mm. (The higher the gauge number, the thinner the needle.) The external diameter of a 32G needle is 0.23 to 0.24 mm, similar to the diameter of a human eyelash.[11]

Early imaging studies of the human skin in the 1980s began to raise concerns about needle lengths being longer than measured depths of SC tissue at different body sites, especially at the thigh, with increased risk of IM injection and subsequent variability in insulin absorption.[12,13] At the time, a perpendicular injection technique without pinch-up of a skin fold was recommended for most people with diabetes.[14] Subsequent imaging studies using ultrasound and computed tomography identified variations in SC tissue thickness in adults and children according to injection site, sex, body mass index (BMI), and age.[9,15-18] A number of other studies in the late 1980s and 1990s characterized the risks of IM insulin injection[13,19] and raised scientific questions regarding

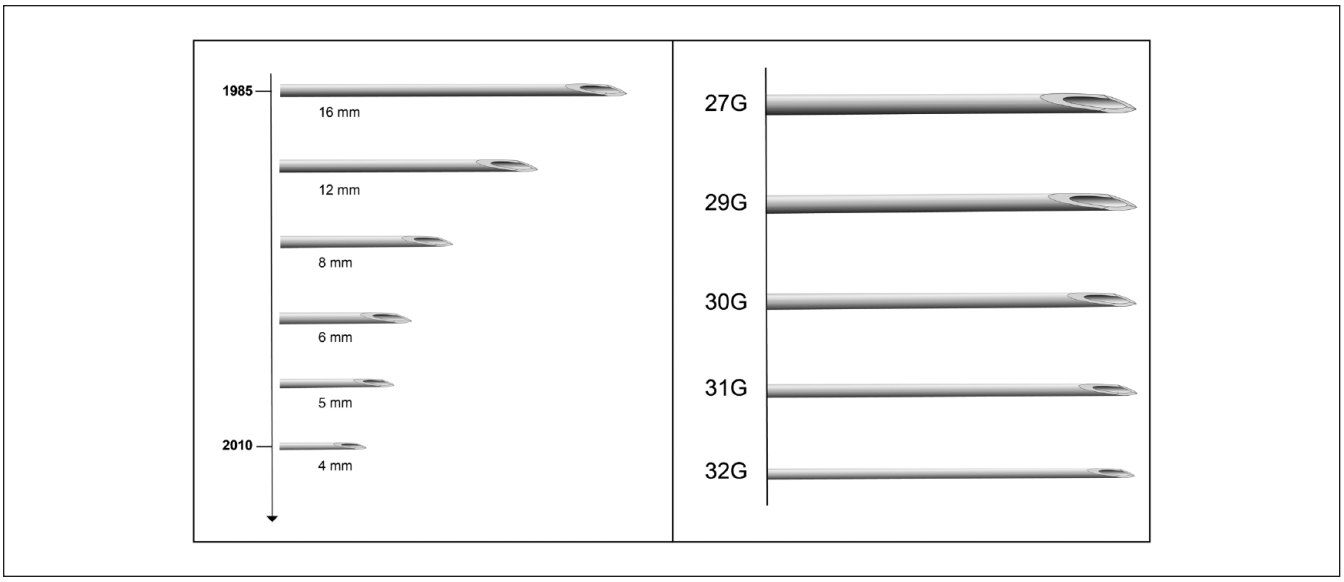


**Figure 1.** Needle evolution over the years: relative lengths and gauges (not actual sizes).

how best to administer insulin SC[16,17] and whether there was variability in the rate of insulin absorption from different injection sites in both obese and nonobese people.[20,21]

For children, the risks of IM injections were particularly pertinent, as they often used the same needle length as adults. Utilizing ultrasound to identify insulin injection locations in children, Polak et al reported in 1996 that 31% of single injections by 59 children delivered the insulin IM.[22] The majority of children were using needles with a length of 12.7 mm and injecting perpendicular to the thigh or arm into a skinfold. Two years later, Birkebaek and colleagues raised the need to individualize injections to 90- or 45-degree angles according to specific injection sites because of variations in skin and SC thickness in children with type 1 diabetes.[17] In addition, they raised a call to action, based on their findings, for development of a 4 mm PN, later supported by the work of Lo Presti et al.[18]

For adults with diabetes, the thickness of skin and SC adipose layers at injection sites was most comprehensively examined by Gibney et al using high-frequency ultrasound.[9] Their study enrolled 388 patients with diabetes (28% with type 1 diabetes) from diverse ethnic backgrounds, in even sex ratios, and ranging in age from 18 to 85 years with BMI ranging from 19.6 to 64.5 kg/m$^2$. Statistically significant differences were observed in both skin and SC thickness for several factors examined, including sex, race, BMI, and body sites. However, the differences in skin thickness were small and considered not clinically significant, with $<$0.6 mm variation among sites in mean skin thickness (from 1.87 mm in the thigh to 2.41 mm in the buttocks). By contrast, mean thickness of SC tissue showed a wider range, with a 5 mm mean difference among sites (from 10.35 mm in the thigh to 15.45 mm in the buttocks). The authors concluded that for most adults a needle length of 4-5 mm inserted at 90 degrees would enter the SC tissue with minimal risk of IM injection.[9] In a follow-up study of 341 people with diabetes analyzing risk of IM injection at usual injection sites for SC insulin (thigh, arm, abdomen, and buttock) the same authors estimated IM injection risks, using a 4 mm needle inserted at 90 degrees without skin pinch-up, of only 1.6% and 0.1% at thigh and abdomen, respectively.[23]

The development of shorter needles was accompanied by the development of needles with smaller diameters (ie, higher gauge number). A Danish study of healthy volunteers published in 2006 compared different PN diameters (23G to 32G) for the frequency and intensity of pain and the occurrence of bleeding using an automated, controlled insertion device.[24] A greater frequency of pain was identified with the larger needle diameters. Use of the thinnest and shortest PN studied (32G x 6 mm) was associated with significantly fewer painful insertions and fewer bleeding insertions as compared with larger gauge needles.[24]

*Needle size and glycemic control.* As needles became shorter and of finer gauges, questions arose whether these needles could present delivery issues, such as leakage and insufficient insulin dose delivery, potentially leading to detrimental effects on glycemic control. A crossover study comparing 2 PNs of 12.7 and 8 mm lengths found no alteration in glycemic control over 9 weeks for obese and non-obese people with diabetes, although a few people, most of them obese, experienced an increase in fructosamine levels after switching to the 8 mm length.[25] Subsequent investigations confirmed that with even shorter needle lengths (4-6 mm), glycemic control remained unaffected in adults with diabetes.[8,26-29] For example, a 4 mm needle length was shown to safely and effectively deliver insulin over 3 weeks for obese and non-obese patients, with equivalent

glycemic control (measured as percent absolute changes in fructosamine) and no difference in insulin leakage as compared with 5 or 8 mm PNs.[8]

The body of evidence regarding needle/PN length for improving insulin delivery from the perspective of the thickness of skin and SC tissue layers was reviewed and recognized in recent guidelines of medical associations, which note that recent evidence supports the effectiveness and tolerability of short needles for SC insulin injections (eg, 4 mm PNs).[30,31]

Limits on further shortening of syringe needles are posed by the need for needles to pass through the rubber seals of insulin vials. Limits on further thinning of needles/PNs include the need to retain sufficient mechanical strength of the needle/PN, while remaining within the bounds of affordability and cost-effectiveness.[32]

## The Patient Perspective

*Impact of needle length and gauge on pain and patient-reported outcomes.* With the availability of shorter needle and PN lengths of 6, 5, and 4 mm, studies that addressed clinical concerns regarding insulin delivery into the SC tissues also introduced new methods of needle evaluation, whereby the patient perspective and PROs were brought more into consideration. Systematic clinical studies investigated the correlation between needle length and gauge and pain perception, as well as patient preferences. Successive generations of shorter needle/PN lengths were associated with lower recorded pain scores in adults: 8 vs. 12.7 mm,[25] 6 vs. 8 mm,[33] 5 vs. 8 or 12 mm,[34,35] and 4 vs. 5, 8, or 12.7 mm needle/PN lengths.[8,28]

In a 1-week crossover comparison between a 32G x 6 mm and a 31G x 5 mm PN, the 32G x 6 mm PN was associated with lower pain scores.[36] In another 1- to 2-week crossover study, a greater percentage of patients preferred a smaller gauge PN tip (32G x 6 mm vs. 30G x 8 mm; 58% vs. 26%, respectively); however, responses for ease of pushing insulin out through the needle favored the larger gauge (30G) PN.[37] The results of these studies suggest that both needle length and gauge can influence injection-related pain and patient comfort.

*Needle and needle tip geometry, hub design.* Additional factors beyond needle length and gauge are known to affect injection pain[32] Thinner needles are intended to reduce injection pain; however, the subsequent decrease in inner diameter may result in more force required to deliver the dose, insulin leakage from the PN tip or injection site, and potentially more frequent needle bending and breaking.

Study of the mechanics of needle insertion indicate that greater force to penetrate the skin is correlated with more frequent pain.[38] An early study of penetration force for needle insertion identified the importance of needle lubrication to reduce drag resistance.[39] Needle sharpness is another important factor, as pain is associated with needle bluntness.[40,41] In addition, the SC tissue counter-pressure on injection has been modeled, with the aim of applying this parameter in needle assessments to ensure that full insulin doses are delivered while minimizing backflow and potentially reducing injection-related pain.[42]

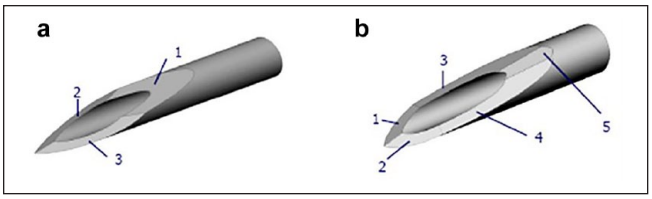


**Figure 2.** (a) Three-bevel needle tip, (b) 5-bevel tip. Reprinted with permission from Hirsch L, Gibney M, Berube J, Manocchio J. Impact of a modified needle tip geometry on penetration force as well as acceptability, preference, and perceived pain in subjects with diabetes. *J Diabetes Sci Technol.* 2012;6(2):328-335.[43]

Bevel design of the needle tip and its impact on penetration force has also been studied extensively. In a 2-part study examining both penetration force and patient-reported pain and preferences in people with diabetes, preclinical force testing in the laboratory measured 23% less mean penetration force for 5-bevel PNs as compared with similar-sized 3-bevel PNs (from 32G x 4 mm to 31G x 8 mm) (Figure 2).[43] In a blinded comparison phase, patients were not able to distinguish between the 2 needle types; however, after short-term home use when informed of the modified design, unblinded patients rated the 5-bevel needles significantly more comfortable, easier to insert, and more preferable, as well as significantly less painful, compared with their usual 3-bevel PNs.[43]

A later study adopted a different approach, using 3-bevel needle tips that were modified asymmetrically; these demonstrated better performance than traditional grind 3-bevel needles in terms of penetration force and pain but were equivalent to a 5-bevel needle.[41] Evaluated in a laboratory setting using a polyurethane substrate, a new 7.5 degree angled 3-bevel PN required less penetration force as compared with standard 11 degree angled 3- and 5-bevel needles; however, patient experiences with the PN were not evaluated.[44]

Design changes to inner walls of the needle lumen have also been introduced to commercially available needles. Leaving the outer diameter of needles unchanged, with a thin-wall needle the inner diameter is increased by 25%, and with an extra-thin wall needle, by >30%.[45,46] The resultant increase in cross-sectional area, estimated as being 60% for the thin-wall needle, enables higher flow rate of the fluid passing the needle and lower plunger pressure resulting from reduced flow resistance.[45] In a comparison of 2 31G PNs with vs. without a thin wall, participants reported significantly less pain over 2 weeks of using the thin-wall PN as compared with the regular-wall PN, and

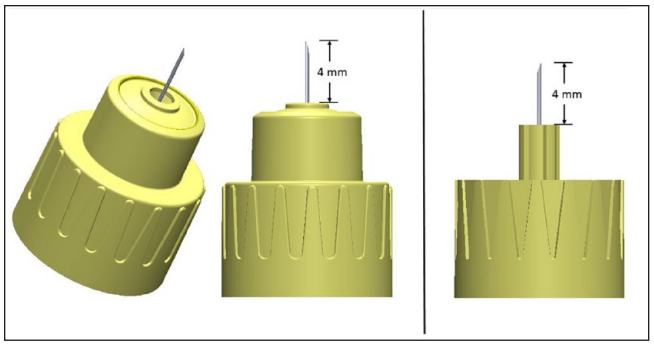


**Figure 3.** Pen needle design of BD Nano™ 2nd Gen (left) and representative conventional posted-hub (right) of comparator devices. The BD Nano™ 2nd Gen PN proprietary surface geometry contains features to first concentrate pressure at the insertion site, and then distribute the applied load upon full engagement with the skin surface. Needles in posted-hub designs extend from a small diameter cylindrical feature 3-4 mm axially from the hub base (BD Nano™ shown at right). Abbreviations: BD, Becton, Dickinson and Company. Reprinted with permission from Rini C, Roberts BC, Morel D, Klug R, Selvage B, Pettis RJ. Evaluating the impact of human factors and pen needle design on insulin pen injection. *J Diabetes Sci Technol.* 2019;13(3):533-545.[48]

more participants expressed an overall preference for the thin-wall PN (78% vs. 8%, respectively).[45] The potential impact of reducing flow resistance during injections was further explored in a 2-part study employing both quantitative and clinical testing of a redesigned extra-thin wall PN incorporating a 5-bevel tip.[46] In quantitative laboratory testing, the extra-thin wall PNs performed significantly better than standard PNs of similar size with respect to thumb force, flow, and time to deliver medication. After 1 week's home use, the extra-thin wall PNs were preferred overall by people with diabetes and rated as requiring less time and less thumb force for injections.[46]

A more recent innovation is a redesigned needle hub, which is the area at the base of the needle shaft (cannula) that attaches the needle itself to an insulin pen. The redesign was motivated by results of studies in humans and animal models recording variations in injection depth associated with the variable force applied against skin during injections.[47,48] The new hub design aims to reduce the impact of variable injection force by dispersing insertion forces across a contoured and expanded surface area (Figure 3).

In a 15-day crossover trial of the extra-thin wall, 5-bevel 32G x 4 mm PN also incorporating the hub redesign, a visual analog scale was used to evaluate overall preference, injection pain, ease of use, overall comfort, and anxiety for needlestick injuries.[7] Participants rated the 32G redesigned PN as less painful, more comfortable, and easier to use, and overall preferred when compared with other 32G PNs of similar length.[7] Specific PN improvements consistently preferred by study participants also included a larger outer needle cover with ergonomically designed grooves for gripping, and a colored, larger, more prominent inner shield. In a subsequent single-visit study, PROs were similarly positive, with less injection pain and less perceived dose delivery force reported for the extra-thin wall, 5-bevel 32G x 4 mm PN as compared with 4 thinner commercially available PNs.[49]

## Injection Technique Education

Injection technique education plays an important role, together with the aforementioned advances in injection technology, in improving patient outcomes and satisfaction.[50] The results of a recent survey conducted in Canada indicate that injection technique was suboptimal among the 230 participants, each of whom was making at least 1 of 7 potential errors in insulin injection technique, most commonly 2 (22%), 3 (27%), or 4 errors (22%).[51] Many participants reported using a smaller than recommended area for their insulin injections (64%), reusing their PNs (39%), or injecting into lipohypertrophic tissue (lumps or bumps under their skin; 37%).[51]

Lipohypertrophy (LH) is a common complication of insulin injections in people with diabetes (both type 1 and type 2), with reported prevalence ranging from 30 to 65% depending on study population.[30,52,53] Predisposing factors for LH development that have been described include small skin area size in which injections are applied repeatedly, failure to rotate injection sites, needle reuse, low BMI (underweight), and use of ice-cold insulin.[54,55] The absorption of insulin when injected into LH lesions may be reduced and inconsistent, frequently resulting in erratic glucose control and hypoglycemic episodes.[53,55] After moving the injections away from LH lesions, insulin doses can be decreased with improved insulin absorption.

Annual examinations by healthcare providers and patient education on insulin injection technique can improve diabetes control and quality of life.[55] Indeed, interventions providing patient education and re-education on proper injection technique, including appropriate site rotation, have resulted in beneficial effects, including improved glycemic control,[50,52,56,57] reduced total daily insulin dose,[57] decreased needle reuse,[52] shrinkage of LH lesions,[52,56] and higher patient satisfaction.[50]

Recommendations for proper injection technique are now published annually as part of the American Diabetes Association Standards of Medical Care in Diabetes.[31] As injection technologies continue to advance, adoption of these recommendations can further enhance the patient experience. In addition, tools such as a recently developed, validated questionnaire to assess insulin injection technique can serve for clinical assessments by physicians and self-assessments by people self-injecting insulin.[58]

## Newer Methods of Insulin Delivery

### *Developments in Insulin Pens*

Further advances to improve the convenience and safety of insulin pens included the development of pens with memory function, first introduced in 2007, followed by the development of "smart pens with connectivity" via Bluetooth or Near-Field Communication. When connected, smart pens automatically record and transfer the dose of insulin injected and calculate insulin "on board"; the data can be shared with connected CGM or flash glucose monitoring devices and digital diabetes management platforms through a mobile app. A recent review noted the lack of studies evaluating clinical outcomes for patients using these pens but pointed out their promise for individualizing therapy and helping people to manage their diabetes.[59]

The emergence of these new technologies, including smart insulin pens, pen caps, attachments, and virtual platforms, can help both patients and healthcare providers to identify and overcome problems such as poor insulin adherence, incorrect insulin initiation and titration, and medication errors.[60] Dissemination of smart pens may increase even further if clinical trials can demonstrate their long-term cost-effectiveness.

### *Novel Route of Insulin Delivery: Intradermal Injections*

The evolution of needle technology has resulted in thin and ultrashort needles (31G and 1-3 mm) designed for intradermal drug application. Delivery of vaccines and therapeutic agents into the dermis, which is well vascularized, enables rapid drug uptake into systemic circulation.[61] Even submillimeter needles can be effective, because the primary barrier to delivery of drugs into the skin is its topmost layer, the stratum corneum, which is just 10 to 40 μm thick. Micrometer scale needles have been developed that are sufficiently long to penetrate through the stratum corneum, yet small enough to cause little or no pain.

Delivery of insulin using such "microneedles" has been demonstrated in diabetic animal models and also studied in people with diabetes, while also in recent years incorporating new production technique such as 3-D printing .[62-65] Intradermal delivery of insulin dramatically accelerates its absorption into the systemic circulation, thanks to the extensive vascular network and arteriovenous shunts in the dermis.[63] A recent review describes advances in glucose-responsive microneedle-array patch systems, so-called "smart patches," together with opportunities and challenges for eventual clinical use.[66]

## Conclusions

The incremental advances in syringe and needle technology seen in the last 100 years—which parallel the advances in insulin and insulin formulations—have not only benefited people with diabetes (taking the "ouch" out of insulin application to a large extent) but have also led to further important innovations for insulin delivery. As insulin therapy for people with diabetes moves toward greater automation of insulin delivery and integration enabled by increasingly smart and connected devices, the continuing study and development of needle and PN technology remains highly relevant.

The worldwide prevalence of diabetes is projected to grow past half a billion patients sooner rather than later, with the greatest increases projected for low- and middle-income countries,[67-69] where expensive and complex insulin delivery systems may not be affordable or practical.[68] Insulin syringes and pens will continue in future to serve as reliable and cost-effective means of insulin delivery for people with diabetes.

### Abbreviations

AID, automated insulin delivery; BD, Becton, Dickinson and Company; BMI, body mass index; CGM, continuous glucose monitoring; G, gauge; IM, intramuscular; LH, lipohypertrophy; PN, pen needle; PRO, patient-reported outcomes; SC, subcutaneous

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