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Review

Influence of Insulin Pen Needle Geometry on Pain Perception and Patient's Acceptability: A Review

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Abstract: Diabetes is one of the most common diseases worldwide, with an increasing number of people affected. Insulin therapy is still the major treatment for both Type 1 and Type 2 diabetes and has evolved from bulky syringes to modern insulin pens introduced in 1985. An insulin pen consists of three major parts: a cartridge, a single-use pen needle (PN), and a precision dosing mechanism. Initially, PNs were long and thick, causing great discomfort and concern. Thanks to advances in design, shorter and thinner needles have appeared on the market, improving patient acceptability and pain perception. Studies highlight the influence of PN geometry and other characteristics on injection-related pain, including length, diameter, bevel design, and hub. Despite a lack of specific international regulations for PN geometry, scientific publications have focused on exploring different PNs' characteristics to optimize patient comfort and reduce pain. To guide the selection of suitable PNs, this review provides a round-up of literature research findings on the impact of PN geometry on pain perception and patient acceptability. Specifically, it provides an overview of the PN manufacturing process, current international regulations, and the state-of-the-art research on PN geometry affecting pain perception.

Keywords: diabetes; injection-related pain; insulin therapy; pen needles

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1. Introduction

Diabetes represents the eighth most prevalent disease worldwide, with a rapidly increasing incidence and detrimental effects on health [1,2]. By 2045, diabetes is predicted to afflict 783.2 million people globally, with middle-income nations having a greater prevalence [3]. Diabetic nephropathy, retinopathy, cancer, heart disease, and foot ulcers and amputations are among the comorbid illnesses often experienced by people with diabetes [4–8]. As a result, due to the high costs and resources required for its management and treatment, diabetes places a significant financial burden on healthcare systems [9].

To date, insulin therapy is the most widely used basic treatment for both Type 1 and Type 2 diabetes for improving glucose control and lowering long-term consequences [10]. Since the discovery of insulin in 1921 [11], several improvements have been made in the methods of its delivery. Insulin was previously administered using wide-diameter needles and plastic or glass syringes [12]. Designed for repeated usage, these instruments needed to be boiled to ensure their effectiveness and safety [13]. Syringes and vials were the only accessible administration method for more than fifty years. However, syringe use frequently led to low accurate dose and poor patient acceptance, resulting in non-adherence to treatment regimens [13]. A new era in insulin delivery began in 1985 when insulin pens became available as an alternative to conventional syringes [14]. Basically, a cartridge of insulin, a single-use needle (henceforth referred to as a pen needle—PN), and a precision dosing mechanism delivering insulin in increments of one unit each click are the three major components of an insulin pen [15]. To date, self-administered insulin therapy using pens is a well-established method for managing diabetes. These functional, simple-to-use devices can reduce injection-related anxiety, thus increasing patient compliance and long-term adherence to insulin therapy [16–18]. Commercially available insulin pens are both reusable and disposable [19]. While reusable pens require the user to insert interchangeable insulin cartridges, pre-filled pens come with an integrated insulin reservoir, disposed of once empty [20].

Particularly, PNs are key components as they serve as both a connection to the injection site and the final route for insulin delivery to the target subcutaneous tissue. At the early stage of insulin pen commercialization, the focus of the needle design was to ensure efficient insulin delivery by deeper penetration into muscle tissues [12]. This required the use of needles with specific dimensions, which are generally expressed in gauge (G), indicative of both inner diameter and wall thickness. Initially, needles intended for basic medical purposes were used to inject insulin. These needles were considerably longer and thicker (generally between 19 and 26 mm in length and with a diameter of 27G—see Table 1) than the PNs used today [21]. Their large size frequently caused great discomfort and concern, especially for children suffering from diabetes. Although a recent review highlighted that PN geometry is just one among twenty-one factors, including product-, injection-, and patient-related factors, contributing to subcutaneous injection-site pain [22], continued attention has been paid to improve PNs' design for reducing pain perception and maximize patient's acceptability. As a result, a wider variety of needles with unique properties have come onto the market. Over time, PNs have evolved to become shorter and thinner, while maintaining sufficient inner lumen to ensure adequate insulin injection [23]. Basically, scientific studies have evidenced that the length and the diameter of the PNs may have a substantial impact on pain perception [24–32]. Other researchers have also explored the role of bevels on the needle tip in reducing injection-related pain [33–37]. Furthermore, advancements in terms of PN hub have been shown to enhance the entire injection experience by reducing discomfort and tissue trauma [38]. Currently, there are no specific international regulations for standardizing PN geometry. Existing regulations focus on needle strength, sharpness, sterility, and compatibility with injection devices, as well as required experimental tests to ensure user safety [39,40]. As a result, the influence of needle characteristics on patient acceptability and pain perception has been the subject of different perspectives in the literature due to this regulatory gap.

Table 1. Corresponding outer diameter for each gauge (G).

Gauge, G	Outer Diameter [mm]
27	0.4128 *
28	0.3620 *
29	0.3366 *
30	0.3112 *
31	0.2604 *
32	0.2350 *
33	0.2096 *
34	0.1842 *

* For these gauge values, a tolerance of 0.0064 mm should be considered.

This review aims to comprehensively summarize findings from research studies available in the literature to understand the impact of insulin PN characteristics on injection-related pain perception, and overall patient acceptance. It specifically considers PN characteristics examined over the years to assess the pain of the injection experience. By offering a thorough review of available research, this knowledge could be useful in guiding the selection of appropriate PNs, thereby improving overall patient satisfaction and quality of life.

This manuscript is organized as follows. First, a brief description of the production process of insulin PNs is given, highlighting their characteristics and geometry. Next, the international regulations applicable to PNs to date are summarized. Section 4 presents the state-of-the-art research on the characteristics of PNs that influence the patient's perception of pain, including PN gauge and length, bevel design, and hub. Finally, we conclude with a summary of the status of this topic, with the aim of offering valuable insights.

2. Insulin PN Characteristics and Geometry

PNs are made of stainless steel, chosen for its durability and ability to resist corrosion, thus ensuring sterilization and sharpness. In addition, stainless steel needles are also resistant to breaking and bending, reducing the risk of damage during use. The standard manufacturing process is known as *drawing.* During this procedure, a stainless-steel tube is drawn through progressively smaller dies to stretch and thin it, refining its diameter and wall thickness. Generally, PNs have a length ranging between 4 mm and 10 mm and a diameter between 27G and 34G. For the sake of clarity, Table 1 details for each gauge the corresponding nominal outer diameter of PNs, expressed in millimeters.

The PN's tip is characterized by several bevels (i.e., angled surface formed at the tip of the needle) rendering it pointed, strong, and sharp and allowing the needle to penetrate easily into the skin and underlying tissues. The geometry of the needle tip is created by starting with the stainless-steel tube, obtained from the drawing process mentioned above, and making sequential cuts on it identifying certain angles. Basically, this process takes place in four main stages [41,42]. In the first stage, the needle's tube is sharpened at a specific angle (reported as δ in Figure 1). Point P represents the highest point where the first grinding plane intersects the outer surface of the tube. In the second stage, this cutting plane is rotated by a bevel angle (reported as φ in Figure 1) while keeping point P fixed, resulting in the second grinding plane. In the third step, the second grinding plane is rotated around the central axis of the needle tube by an angle, β, and moving the point P by a length l, resulting in the third grinding plane. This represents the first of the two lancets forming the needle tip. Rotating this plane by 2β in the opposite direction yields the second lancet forming the needle's tip.

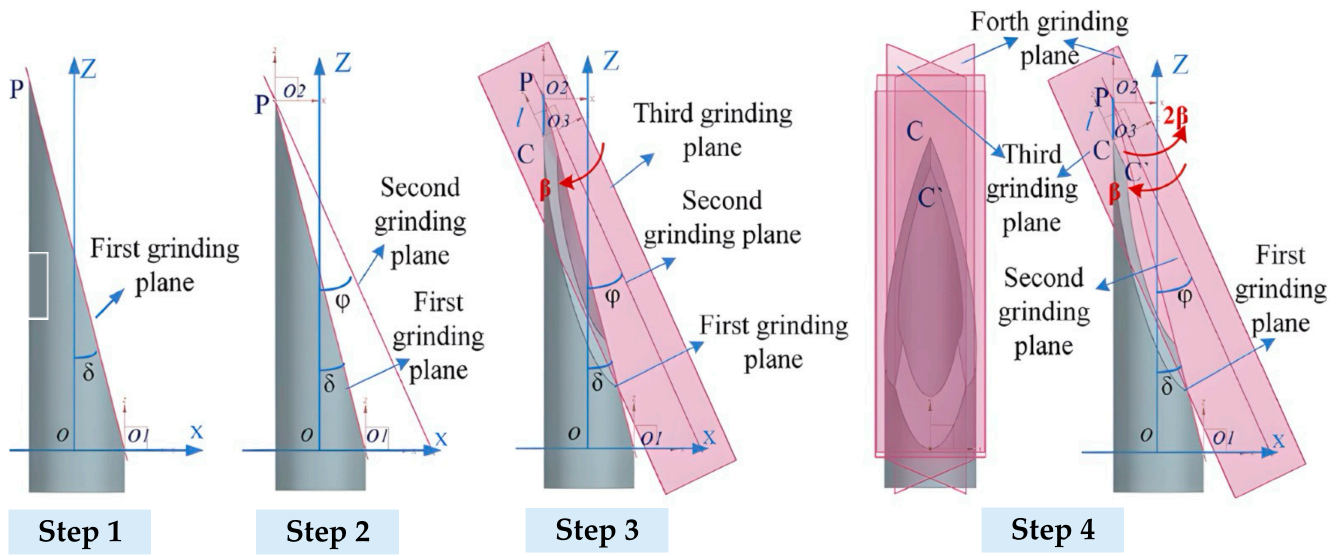

Figure 1. Schematic representation of the four main steps involved during the manufacturing process of PNs (adapted from [41]).

The needle tip, processed in this way, turns out to have three bevels, which has been the standard of needle point geometry for many years. Today, however, PNs with a geometry of even more than three facets (needles with 5, 6, or even 7 bevels) as well as further geometric differences to standard needle tips can be found on the market [42–45].

3. International Regulations Related to PNs

To date, the international regulation relevant to PNs for insulin delivery is ISO 11608-2:2022, titled *Needle-based injection systems for medical use. Requirements and tests methods. Part 2: Double-ended pen needles* [39]. Part of this regulation focuses on the materials, size, and mechanical characteristics of needle tubes, ensuring that they are suitable for their intended use without causing tissue damage. The materials must comply with ISO 9626:2016, *Stainless steel needle tubing for the manufacture of medical devices. Requirements and test methods* [46], thus ensuring the biocompatibility and strength necessary for their safe use. In addition, the characteristics of the tubes must meet specific requirements that ensure their functionality. Moreover, needle points must be sharp and free of visible defects, such as feathered edges or burrs, to minimize pain and discomfort during insertion. In addition, needle surfaces should be smooth and free of foreign particles or visible lubricants to ensure no contamination during use. The standard also describes requirements for flow rate through the needle, both for tapered and non-tapered needles. A minimum flow rate is specified to ensure that the drug can be administered effectively. The bond between the hub and the needle tube is another critical aspect covered by the standard. The strength of the bond must be verified through specific test methods to ensure that the needle does not accidentally detach during use. The minimum bond strength is determined based on the metric dimensions of the needle, ensuring that it is strong enough for the intended conditions of use. The standard also includes guidelines for conditioning needles in different environmental conditions, such as dry heat, cold storage, and humidity, to ensure they maintain their properties in various situations. Detailed test procedures are provided to verify the robustness of the product. Lastly, it also describes in detail the experimental tests to be performed for verifying adherence to the standard in terms of performance and safety requirements for user.

A further relevant international standard is UNI EN ISO 7864:2016, *Sterile hypodermic needles for single use—Requirements and test methods* [40]. This regulation is applicable to hypodermic needles in general and describes the requirements for needle tip geometry. The standard reports that the PNs usually present a primary bevel angle of $11^\circ \pm 2^\circ$, although there are several modifications also allowed, such as a short bevel angle of $17^\circ \pm 2^\circ$. Moreover, it describes the procedure, instruments, and methods required for measuring the penetration force of hypodermic needles. Scientific studies focusing on the comparative evaluations of different PNs generally refer to ISO 7864 for carrying out mostly standardized and repeatable testing to evaluate penetration force. The testing protocol involves the insertion of the needle into a specific substrate at a constant speed of 100 mm/min, while recording the force values as a function of needle advancement. The needle must be inserted into the substrate for a penetration depth equivalent to 80% of the nominal length. For example, a 4 mm needle must be inserted 3.2 mm (i.e., 80% of 4 mm) into the substrate during testing. A new insertion point in the substrate must be used for each penetration test. During testing, both the penetration force and the friction force are measured. As shown in Figure 2, it is possible to observe that the force trend increases up to a maximum value (i.e., penetration force), which represents the maximum force value required to pierce the substrates and depends on the geometry of the needle tip. Once the substrate is pierced and provides less resistance, the force gradually, or abruptly, decreases and remains almost constant around a force value as the needle continues to move. This force value, indicated as friction force, primarily depends on the lubrication of the needle's shaft and not on the geometry of the tip, as the needle tip has already passed through the substrate.

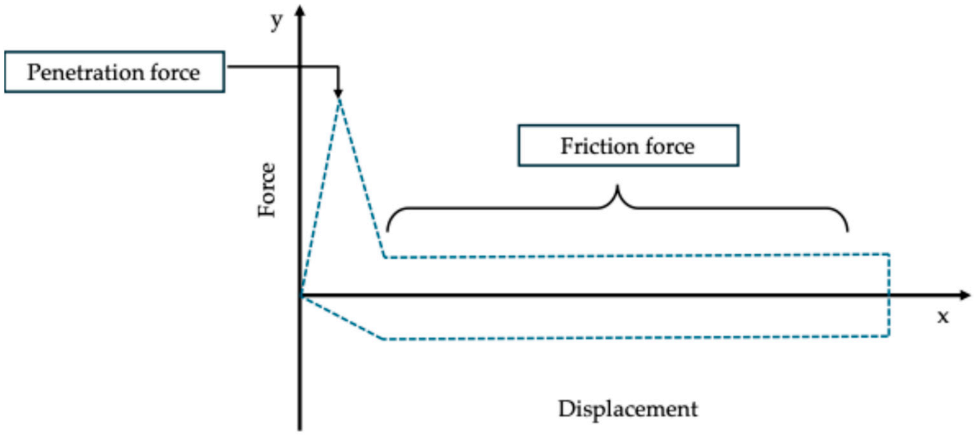

Figure 2. Exemplary force trend as a function of displacement obtainable during mechanical test regulated by ISO 7864, detailing the penetration and friction.

It is also crucial to emphasize that, in order to reduce pain, guidelines from a number of diabetology societies and associations, such as the Italian Society of Diabetology, the American Diabetes Association, and the European Association for the Study of Diabetes, place a strong emphasis on the diameter and length of PNs. To enhance the injection experience and lessen discomfort, they advise using thinner, shorter PNs [47,48].

4. PN Characteristics Influencing Pain Perception: State-of-the-Art

4.1. PN Gauge and Length

One of the first studies investigating the impact of PN gauge and length was published in 2000 by Hanas et al. [49]. The authors evaluated six PNs, each differing in gauge (27G, 28G, 29G, and 30G) and length (ranging between 8 mm and 13 mm) in 100 young patients affected by Type 1 diabetes. Specifically, the research was divided into two studies, A and B. In Study A, 60 participants used three different PNs: 27G and 13 mm in length, 28G and 13 mm in length, and 28G and 12 mm in length. In Study B, 40 participants used the other three needles: 28G and 12 mm in length, 29G and 13 mm in length, and 30G and 8 mm in length, along with a placebo injection (no needle). Pain was assessed using a visual analog scale (VAS). Both study A and study B showed no significant difference in terms of pain perception between PNs, suggesting that thinner PNs do not necessarily provide a better experience in terms of pain. Similarly, a few years later, a study by Schwartz et al. [50] reported that, compared two PNs (31G and 6 mm in length needle vs. 29G and 12.7 mm in length) in 62 obese patients affected by Type 1 and Type 2 diabetes showed pain scores comparable between shorter and longer PNs.

In 2006, a study carried out on healthy volunteers by Arendt-Nielsen et al. compared PNs of various gauges (from 23G to 32G) in terms of frequency of pain, pain intensity (measured using the visual analogue scale—VAS), and bleeding occurrence following needle insertions with an automated needle injection system. The findings showed that needles with a larger diameter were associated with more frequent pain, whereas thinner and shorter PNs (32G and 6 mm in length) resulted in significantly fewer painful injections and less bleeding [32].

A 2009 study funded by Novo Nordisk compared individuals' preferences for two PN types: NovoFine® 30G tip, 8 mm long, and NovoFine® 32G tip, 6 mm long (Novo Nordisk A/S, Bagsvërd, Denmark) [24]. Specifically, the NovoFine® 32G needle employed thin-wall technology and a narrow tip and aimed to enhance injection comfort. Participants in the clinical trial included patients with both Type 1 and Type 2 diabetes. The research set out to assess patient perceptions of pain, injection pressure, handling, and acceptability of the two needle types used to inject insulin. Pain perception during insulin injection was low for both needles, with the NovoFine® 32G tip needle associated with even lower pain scores, particularly when injecting into the abdomen or thigh. Needle bending was infrequent, with a slightly higher occurrence for the 30G needle, possibly due to its longer length.

The comfort of the NovoFine® 32G needle, 6 mm long (Novo Nordisk A/S, Bagsvërd, Denmark) and Micro Fine Plus® 31G, 5 mm in length (Nippon Becton Dickinson Co., Ltd., Tokyo, Japan) in insulin-treated diabetic patients was the subjects of a randomized, cross-over study [25]. The two needles share the same inner diameter (i.e., 0.25 mm), while they had a different external diameter at the tip (i.e., 0.23 mm for NovoFine® 32G and 0.25 mm for Micro Fine Plus® 31G), as highlighted in Figure 3. The study included 30 patients (24 men and 6 women) with at least 3 months of insulin self-injection experience. Two groups of patients were randomly assigned to use either NovoFine® or Micro Fine Plus® needles for one week before switching to the other set of needles for an additional week. Overall, patients expressed greater satisfaction with the NovoFine® compared to the Micro Fine Plus® needles, with significantly higher scores for NovoFine® in all questionnaire items (except one). There was less reported fear, less discomfort during insertion, and less bleeding and bruises when using NovoFine® needles. Evaluation of factors such as insulin leakage, needle removal, and button pressing power also favored the NovoFine® needles. The smaller diameter and tapered shape of the NovoFine® positively affected patients' comfort and satisfaction, despite the needles being longer.

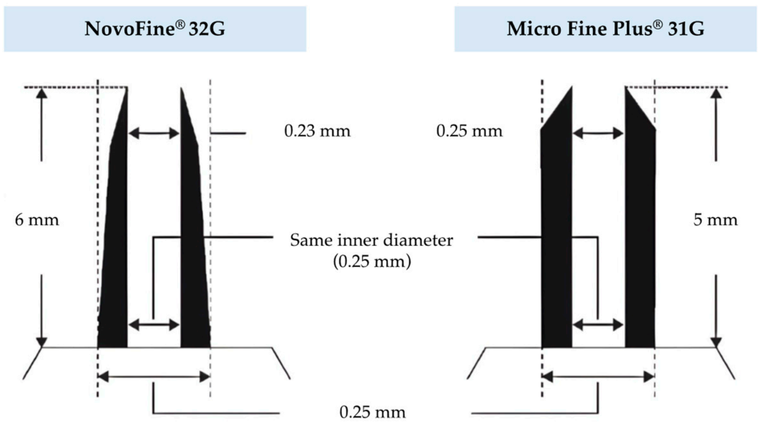

Figure 3. Comparison between the NovoFine® 32G 6 mm long needle and the Micro Fine Plus® 31G 5 mm long needle (originally published by [25], adapted and used with permission from Mary Ann Liebert, Inc. publishers).

A comparative study of the usage and safety of two PNs was carried out in 2015 by Yamada et al. [26]: an extra-thin wall 32G needle, 4 mm long (BD Ultra-Fine™ Nano™-UF32G-, Becton-Dickinson and Co., Franklin Lakes, NJ, USA) and another PN of the same length but 34G (NANOPASS® NEEDLE II- NP34G-). The authors proposed a prospective, randomized, controlled home-use crossover study. A total of sixty patients were enrolled, using the two PNs in a crossover manner for a week, recording adverse events and evaluating usability after two weeks. Evaluation criteria comprised ease of pushing the injection button, penetration pain, smooth insertion, pain during insulin delivery, and overall preference, measured using a 150 mm VAS. Significant gender differences in maximum force were noted, with higher values in males than in females (91.7 N ± 22.3 N vs. 57.4 N ± 14.9 N). The usability evaluation showed that NP34G was favored for smooth insertion and pain during insulin delivery, although no significant differences were found regarding other aspects. The UF32G needle, designed to reduce injection pressure, showed no significant difference in ease of pushing an injection button compared to NP34G, possibly due to subjects having enough thumb force for routine insulin injection.

A randomized trial reported by Hirsch et al. was aimed at comparing a 32G PN, 4 mm in length, with two marketed PNs (i.e., 31G with 5 mm and 31G with 8 mm) manufactured by BD (Becton-Dickinson & Co., Inc., Franklin Lakes, NJ, USA) in terms of injection-related pain [27]. The study involved a total of 173 participants, grouped into 'low dose' and 'regular dose' categories based on their insulin usage, alternated between the 4 mm needle and either the 5 mm or 8 mm needles over two three-week periods. Pain perception was evaluated using 150 mm VAS, where participants marked their pain level after each injection, ranging from "much less painful" to "much more painful" with a midpoint of "no difference". The results indicated that the 4 mm PNs was preferred by about two-thirds of participants for causing significantly less pain and requiring less force for injection. The study highlighted the potential of the 4 mm needle to improve comfort and preference in insulin therapy without compromising safety or effectiveness. However, it is important to highlight that both the researchers and participants were aware of the needle being used, which may have introduced bias into the results, particularly in subjective assessments such as pain and preference.

Two distinct types of PN from Pikdare (Pin Insupen, 33G vs. 32G, both 4 mm in length) were assessed in a cross-over randomized experiment in 2014, with an emphasis on pain, safety, and metabolic regulation [28]. Each patient used each needle for three weeks during their six-week participation. Pain was assessed using VAS. The results showed that the 33G needle was associated with less pain. A few years later, another randomized, two-period cross-over study funded by Pikdare was conducted to compare a new 34G needle, 3.5 mm in length, with a 32G needle, 4 mm in length (Pic Insupen from Pikdare) in patients affected by Type 1 and Type 2 diabetes [29]. Both males and females were recruited from eight different diabetic clinics. As was done for [28], the study evaluated different parameters, including metabolic control, insulin leakage, and safety. Additionally, patients were asked to evaluate their pain using VAS. The outcomes highlighted no statistical differences between these two needles in terms of pain during needle insertion and during injection.

Two randomized, partially single-blinded studies [30] compared user experiences between a second-generation 32 G extra-thin-wall, 5-bevel cannula PN and four commercially available PNs of similar lengths but thinner diameter (i.e., 33G and 4 mm, 34G and 4 mm, 34G and 3.5 mm). The proposed study enrolled adults (aged between 18 and 75 years old) with Type 1 or Type 2 diabetes and who had at least three months of experience with insulin pens. In the first study, the new 32G PN was compared with three of the four thinner needles (ranging from 33G to 34G and lengths of 3.5 mm to 4 mm), while in the second one it was compared only with a PN of 34 G, 4 mm long. Participants performed a total of 12 abdominal injections in 6 pairs, each pair including one injection with the investigational 32G PN and one with a comparator PN, in random order. After each injection pair, participants compared injection pain via 150 mm VAS and perceived dose delivery force via a relative 5-point Likert scale. The results showed that the investigational BD 32G PN caused significantly less pain and required less force compared to the thinner ones. However, it is noteworthy that the studies were carried out under supervised conditions, which may limit the applicability of the findings to unsupervised real-world settings. Furthermore, while participants were only partially blinded, the investigators were aware of the needle identities, potentially introducing bias. The study's focus on abdominal injections may also limit the generalizability of the results to other injection sites.

The research proposed by [31] aimed to compare traditional PNs with safety PNs, which included a retractable shield to prevent accidental needle stick injuries (DropSafe®, HTL-Strefa S.A., Ozorków, Poland), with a length of 6 mm and 31G, identical to the conventional ones. Specifically, 72 adolescents and young adults aged 14–18 with Type 1 diabetes were involved in a prospective, single-center study (54.2% male and 45.8% female). Participants were shifted from conventional needles to safety PNs for 12 weeks. Then, they were invited to assess safety PNs using a usability scale comprising 14 questions covering six key domains—pain and fear associated with the needle's appearance, the ease of installing and removing the needle, pain and discomfort during needle insertion, bleeding and bruising at the injection site, insulin dribbling, and the effort required to press the injection button—culminating in an overall satisfaction rating. Every question was scored using a 10-point VAS, with higher scores denoting better results. The obtained results emphasized the positive impact of safety PNs in terms of perceived pain, usability, and safety.

4.2. Bevel Design

In 2012, research published by employees from Becton Dickinson aimed to evaluate the differences between PNs characterized by 3 and 5 bevels (see Figure 4) in three different sizes: 32G, 4 mm, 31G, 5 mm, and 8 mm PNs [33]. First, a preclinical evaluation was carried out in a laboratory environment through a testing machine. The tests evaluated the penetration force applied to a substrate designed to mimic skin tissue. The results showed that the average penetration force was 23% lower in the case of 5-bevel PNs compared with 3-bevel ones. However, during the clinical trial, eighty-six of the patients enrolled were unable to distinguish the two different kinds of PN (3-bevel vs. 5-bevel), and neither were they able to distinguish which one was less painful.

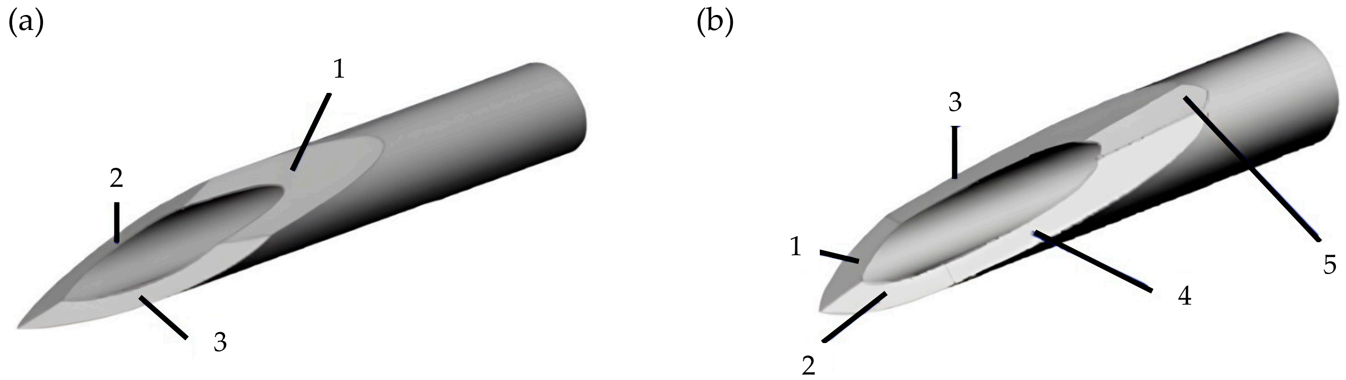

Figure 4. Schematic representation showing (**a**) 3-bevel PN tip vs. (**b**) 5-bevel PN tip (originally published by [33], adapted and reprinted with permission of Sage Publications.).

A few years later, in 2016, another study, funded and authored by Novo Nordisk, further explored how different needle designs affect the comfort of insulin injections [34]. The study was a single-blind trial involving 30 subjects. Participants were invited to test with 18 different types of needles, showing different diameters and number of bevels (between 1 and 5). In particular, the study compared standard 3-bevel needles—typically used as a reference—with other designs, including asymmetrical 3-bevel, 5-bevel, short-tip, and 1-bevel needles. A key finding was that the asymmetrical 3-bevel tip (34G) and the 5-bevel tip (32G) both exhibited similar penetration forces, outperforming the traditional 3-bevel design. It is important to note, however, that the differences in needle diameter between these two PNs may have influenced their performance.

In 2019, Leonardi et al. from Pikdare proposed an improvement in standard 3-bevel PNs by introducing a primary bevel with a lower angle (7.5° compared to the standard 11°, as highlighted in Figure 5) [35]. Then, they investigated different PNs characterized by different diameters (i.e., 31G, 32G, 33G, 34G) and length (3.5 mm, 4 mm, 5 mm, and 8 mm), and characterized by 3-bevel and 5-bevel tips in terms of penetration and friction forces. Experiments were carried out in a laboratory environment by means of a testing machine and in accordance with ISO 7864. The results showed that the innovative needle, with its lower primary bevel angle, required less penetration force than conventional needles of the same diameter that had three or five bevels and an 11° standard cutting angle. Furthermore, this new needle's sliding force was equivalent to that of 5-bevel needles.

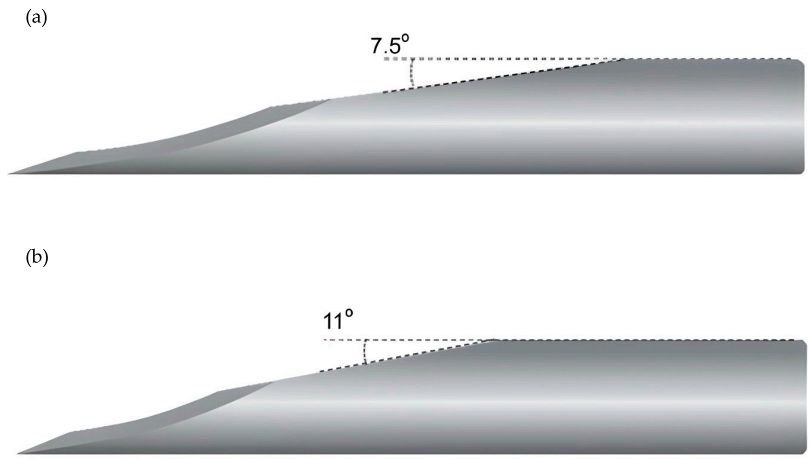

Figure 5. (**a**) 3-bevel PN tip with a primary bevel of 7.5°; (**b**) Standard 3-bevel PN needle with a primary bevel of 11° (Medical Devices: Evidence and Research 2019:12 311-317—Originally published by [35], adapted and used with permission from Dove Medical Press Ltd).

Jushiddi et al. explored the impact of bevel angles on the performance of hollow needles used during conventional medical procedures such as biopsies, by means of a computational model and experimental tests [36]. The primary objective of the study was to understand how different bevel angles affect needle deflection, insertion forces, and contact stress distribution during insertion into a mimetic soft-gel that simulates biological tissue. The needles tested had bevel angles of 15°, 30°, 45°, 60°, and 90° blunt with 22G, all custom-made. A gel compound made of agar was employed to mimic the characteristics of biological tissue, such as pork liver. A mechanical testing system was used to insert needles into agar compound at a constant speed (i.e., 2.5 mm/s) and a penetration depth of 40 mm. Both the computational model and the experiments showed that needles with lower bevel angles (15° and 30°) exhibited larger deflections compared to needles with higher bevel angles (60° and 90°). However, the insertion force did not vary significantly across different bevel angles. Lower bevel angle needles also experienced higher contact stress values due to their sharper cutting edges, leading to larger initial peak forces during insertion. This comprehensive analysis of bevel angles provides valuable information for the design of medical needles, potentially improving clinical outcomes for various procedures involving needle insertions.

A recent study reported by [37] investigated how the number of bevels on the tip of PNs affects the forces and energy involved in the injection process. The intention was to find out if the forces and energy needed for needle insertion and extraction could be reduced by using more bevels. Two types of needles were used for the experiments: 31G, 5 mm in length, and 32G, 4 mm in length. For both types, comparisons were made between 3-bevel and 5-bevel needles. Each type of needle underwent fifty measurements of testing on rubber substrates. Plunge force, drag force, and extraction force were among the forces measured during the insertion–extraction cycle. Additionally, the cycle's energy was computed. The results showed that 5-bevel needles consistently required lower drag and extraction forces compared to 3-bevel ones. Specifically, the drag force for the 31G, 5 mm long needle was significantly lower ($p = 0.040$), and for the 32G, 4 mm long needle it was even more significant ($p < 0.001$). The extraction force was significantly lower for both 5-bevel needle types ($p < 0.001$). Moreover, the energy required for the insertion–extraction cycle was significantly lower for 5-bevel needles across both needle types ($p < 0.001$). However, it is important to note that, from one side, as reported above, drag and extraction forces do not depend on bevel design; moreover, there is no scientific evidence supporting the relevance of the energy parameter in assessing patient comfort, perceived pain, or other aspects related to needle interactions. In fact, the cycle (force-displacement) obtained from in vitro tests is performed by perforating a substrate, cited in the standard [38], which can also be very thin (down to 50 µm), which is not representative of the energy exchanged in a real situation with body perforation. Moreover, if we examine the graphs in Figure 6, assuming they represent experimental tests conducted on two different PNs showing the same energy exchanged (i.e., colored areas are identical), we can observe that the needles exhibit distinct penetration and friction forces. Despite these differences, if the energy parameter was considered significant, two needles with very different performance characteristics, such as those depicted in the blue and orange graphs, would be evaluated as identical, highlighting the lack of energy parameter relevance in assessing needle performance.

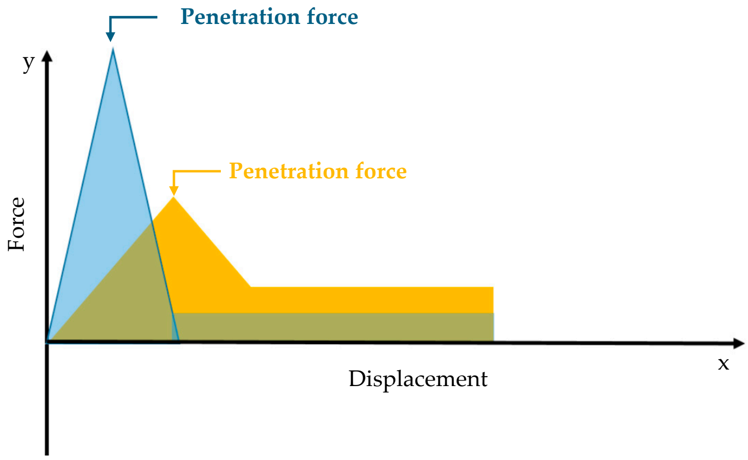

Figure 6. Comparison of penetration and friction forces between two different pen needles. The blue graph represents one needle, whereas the orange graph represents another.

4.3. PN Hub

The preclinical, in vivo investigation put out by [38] assessed the effects on needle penetration depth (NPD) of various PN hub designs and force exerted against the skin during injection. A comparison was carried out between four PNs, each measuring 32G and 4 mm in length. Specifically, the BD NanoTM Ultra-FineTM, Clickfine®, and Unifine® Pentips® posted-hub designs were compared with a newer hub design, BD NanoTM 2nd Gen. Specifically, the BD NanoTM 2nd Gen's hub was conceived for equally distributing pressure once the needle is fully inserted, concentrating it at the insertion site, thus minimizing the variations in penetration depth caused by variations in the force exerted during injection. Traditional hub designs, on the other hand, use a tiny cylindrical extension from the base of the needle to support it. This design typically leads to greater variability in penetration depth, especially if the applied force is not consistent, potentially impacting the safety and effectiveness of the insulin delivery. The study employed preclinical, in vivo experiments using a porcine model to evaluate NPD and erythema scores at various clinically relevant skin application forces. The results indicated that the BD Nano™ 2nd Gen PN design demonstrates shallower and more consistent needle penetration than other hub designs over a range of applied forces. Furthermore, the authors calculated the potential risk of unintended IM injections based on the measurements of skin thickness and subcutaneous tissue at common injection sites. The study found a significant reduction in calculated IM risk for the BD Nano™ 2nd Gen design compared to the affixed hub designs, suggesting that hub design, along with injection technique, plays a crucial role in determining the accuracy and consistency of needle depth. While the study highlights the differences in needle penetration depth between PN hub designs, it does not delve into the specific design elements contributing to these differences, leaving certain aspects unexplored. It is worth noting that the study evaluated only a small cohort of PN hubs, significantly limiting the general applicability of the results. Moreover, the swine model may have limitations in fully replicating the complexities of human skin and injection procedures.

5. Discussion and Conclusions

In the context of insulin therapy for diabetes management, this review highlighted the important influence of PN characteristics on pain perception and patient acceptability. Despite the inherent challenges in objectively quantifying pain due to its subjective nature and the variability among individual responses, significant progress has been made in the design of PNs. These advancements represent continuous attempts to enhance the patient experience in diabetes management by reducing pain and improving comfort for users. The key factors influencing pain perception include PN length, gauge, the number of bevels, and the tip and hub design [24–31,33–38].

Despite these advancements, there is a lack of specific international regulations standardizing the geometry of PNs. Current regulations primarily address needle strength, sharpness, sterility, and compatibility with injection devices [39,40], which has led to varied approaches in PN design [12].

Considering the different types of PN available on the market today, this overview allowed us to broaden the knowledge of how these parameters affect patient's perception, with a focus on insulin injection. Through the analysis of these characteristics, the research successfully extended our understanding of how PN design influences patient's pain perception and acceptability. In summary, while clinical trials such as the ones proposed in [49,50] found no significant difference in terms of pain perception with shorter and longer PNs, others research reported that PNs with a higher gauge and shorter length reduce discomfort and improve patient adherence to treatment [24–32]. These findings underscore the inherent challenges and variability in assessing pain perception through in vivo studies. However, it is important to highlight that, to date, international recommendations and Italian diabetic guidelines support PNs of shorter length and thinner diameter as the recommended option for patients [23,47,48].

While standard criteria like gauge and needle length have been largely investigated, other design features such as thin-wall technology, emerging from the investigation reported by [24], seem to also have an impact on patient experience. Indeed, thin-wall technology increases flow rates without compromising the outer diameter of the needle, thus reducing injection time and minimizing pain. Additionally, innovative bevel designs, such as 5-bevel PNs, appear to reduce penetration forces compared to traditional 3-bevel ones [33,37]. However, it is noteworthy that the opinions regarding the optimal number of bevels are still controversial [34,35]. With a soft-sharpening needle with a novel 3-bevel design, the PICASSO study [35] stands out as an innovative and most up to date one analyzing the impact of bevel number and primary bevel angle on pain perception. Unlike other researchers in the field of bevel design [33,34,37], the PICASSO study objectively evaluated the impact of these geometric characteristics through mechanic tests in a laboratory environment in accordance with ISO 7864 [35]. Although more recent than [35], a study claimed the superiority of 5-bevel PNs over traditional 3-bevel ones by comparing PNs that also differed in diameter and length [37]. However, in this study, mainly drag and extraction forces showed significant differences, although these forces do not depend on the geometry of the needle tip; moreover, the energy parameter computation served as the basis for the performance rating, which lacks significant relevance in assessing patient comfort or perceived pain. Indeed, as shown in Section 4.2, PNs with very different performances could be comparable in terms of energy.

Moreover, one study underlined the critical role of the hub design, emphasizing that modern hubs for uniformly distributing pressure provide more constant needle penetration depth and minimize tissue trauma [38].

Currently, the predominant methods in the literature for quantifying pain rely largely on subjective measures such as VAS [26,28,30–33,49]. While VAS is a well-established approach for assessing patients' self-reported pain in clinical practice, its subjectivity may compromise the objective assessment of needle performance. In contrast, very few studies have focused on the measurement of penetration force [33–35], although this method offers more reliable and comparable data, which is currently lacking in the existing literature. Based on the findings of this review, it is evident that the mechanical tests for penetration force outlined in ISO 7864 should be considered the benchmark for assessing the impact of PN characteristics on pain perception. This methodology offers a more objective approach to data collection, crucial in reducing the influence of the wide range of variables encountered in in vivo studies, such as anatomical variability among patients and the ongoing debate over the impact of PN geometric characteristics on patient comfort. By increasing the focus on in vitro studies carried out in controlled environments, we can provide a consistent and reliable basis for evaluating and improving needle design.

In conclusion, this comprehensive review highlights the need for additional studies to improve PN design and offer universal standards. These developments have the potential to greatly enhance treatment adherence, efficacy, and the quality of life for diabetic patients by enhancing the injection experience. Overall, this overview offers insights into the crucial role of PN geometry's characteristics regarding pain and patient's acceptability, thus helping to guide healthcare professionals and manufacturers in the selection and development of the most suitable PNs for effective diabetes management.

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