diabetology

MDPI

Review

The Use of Insulin Pen Needles: The Italian Society of Metabolism, Diabetes, and Obesity (SIMDO) Consensus

Giancarlo Tonolo [1,*], Ariella DeMonte [2], Maria Antonietta Taras [1], Alessandro Scorsone [3], Patrizio Tatti [4], Battistina Pittui [1], Salvatore Turco [5] and Riccardo Trentin [6]

[1] Department BIA for Chronic Diseases and Diabetes Operative Unit, ASL Gallura, 07026 Olbia, Italy; giancarlo.tonolo@aslgallura.it (G.T.); anto.ta@inwind.it (M.A.T.); battistina.pittui@aslgallura.it (B.P.)
[2] Coordination of Clinical Networks, Department of Clinical Governance, Regional Healthcare Coordination (ARCS), Friuli-Venezia Giulia, 33100 Udine, Italy; ariella.demonte@asugi.sanita.fvg.it
[3] Complex Operative Unit for Internal Medicine, Regional Referral Centre Diabetes and Pump Devices, Civico-Partinico Hospital (PA), 90047 Partinico, Italy; alexscorsone@gmail.com
[4] Operative Unit for Diabetes and Endocrinology, Italian Neuro-Traumatology Institute, 00046 Grottaferrata, Italy; info@patriziotatti.it
[5] Fernicola Marano Antidiabetic Centre of Naples, Naples 2 Local Health Authority, 80016 Naples, Italy; turcosalvatore48@gmail.com
[6] Rete Sarda Diabete, Association of Diabetic Patients in Sardinia, 09016 Iglesias, Italy; riccardotrentin71@gmail.com
* Correspondence: giancarlo.tonolo@aslgallura.it

Abstract: A correct injection technique is essential in order to ensure the effectiveness of insulin and to achieve good metabolic control, and the use of suitable needles is fundamental. Today, technological evolution has transformed insulin needles into innovative tools able to guarantee an effective and safe administration of insulin, to reduce local complications, such as lipodystrophies that are an obstacle to the effectiveness of the treatment itself, and to minimize the pain of the injection, a crucial factor in the acceptance of therapy and for compliance. The steering committee of the scientific society SIMDO has commissioned the scientific committee and some members of the board to draw up an official SIMDO point of view/consensus on the use of insulin needles. In this way, a group that has combined the experience gained in their field of expertise—diabetologists operating in the public and private sectors, nurses, psychologists, and patients—was set up. The aim is to give indications regarding insulin injection techniques, combining themes such as technology innovation, education in self-management, and psychological support for the patient into a unified approach based on the priority area of patient quality of life. The document will provide operational recommendations that integrate the directions regarding the standards of care for diabetes resulting from the most recent scientific acquisitions with the concept of quality at 360°, as it emerged from the point of view of all the operators involved, but with the patient's interests as a central focal point.

Keywords: diabetes; insulin injection; diabetic complications

Citation: Tonolo, G.; DeMonte, A.; Taras, M.A.; Scorsone, A.; Tatti, P.; Pittui, B.; Turco, S.; Trentin, R. The Use of Insulin Pen Needles: The Italian Society of Metabolism, Diabetes, and Obesity (SIMDO) Consensus. *Diabetology* **2024**, *5*, Firstpage–Lastpage. https://doi.org/10.3390/xxxxx

Academic Editor: Paulo Matafome

Received: 21 May 2024
Revised: 25 June 2024
Accepted: 28 June 2024
Published: date

1. Introduction

***Drugs do not work in patients who do not take them.*"** An aphorism as simple as it is indisputable for the truth that it expresses and that nevertheless should continue "as well as in those who do not take them well," considering that adherence to treatment and a correct administration contribute decisively to the success of medical therapies. This is particularly true in a chronic disease such as diabetes, in which even today, the cornerstone of treatment for a significant share of patients is represented by insulin therapy and the need for daily (often multiple) injections indefinitely. This requires learning and applying the correct inoculation technique while also involving discomfort that heavily influences the patient's quality of life and adherence to treatment. A correct injection technique is essential in order to ensure the effectiveness of insulin and to achieve good metabolic control, and the use of suitable needles is fundamental. Today, technological evolution has transformed insulin needles into innovative tools able to guarantee an effective and safe administration of insulin, to reduce local complications, such as lipodystrophies that are an obstacle to the effectiveness of the treatment itself, and to minimize the pain of the injection, a crucial factor in the acceptance of therapy and for compliance. However, there remain unclear sides that are not completely covered by the literature since no guidelines are available so far. Drawing up guidelines in the world of needles for insulin administration finds, among the obstacles, the possibility of performing multicentre trials with clear outcomes, a large number, and adequate observation time. With this view, the steering committee of the scientific society SIMDO (Societa' Italiana Metabolismo Diabete Obesita'(www.simdo.it, accessed on 24 June 2024) has commissioned the scientific committee and some members of the board to draw up a consensus statement/point of view on the way insulin needles. Thus, a group of people with experience gained in their field of expertise—diabetologists operating in the public and private sectors, nurses, psychologists, and patients—was set up. The aim is to reach a consensus mainly around the aspects of technology and innovation, psychological and educational support for the patient, into a unified approach based on the priority area of patient quality of life, with the patient's interests as a central focal point. Operatively, each author independently collected a bibliography on the various topics proposed (technology, psychological aspects of the puncture, and educational aspects). The outline of the work was drawn up after numerous meetings, both face-to-face and via the web, in order to decide on the writing line. The first draft of the work was prepared by GT, AD, and MAT, and then each author subsequently made modifications and changes. The final work was presented at the 2023 National SIMDO meeting (Naples, 12–14 October 2023) to all associates in order to receive feedback on it.

2. Technological Evolution of Insulin Pen Needles

Throughout the course of the last few decades, innovation in terms of diabetes has involved multiple aspects regarding both treatment and glycemic monitoring. One of these concerns the devices required for hypoglycemic and insulin therapy and beyond, which are administered subcutaneously.

The technological evolution regarding insulin pen needles has for a long time been focused upon the length and external diameter of the cannula; these are technical characteristics that significantly contribute to acceptance and adherence to multi-injection therapy, despite not being the only ones to have a role in that sense. Originally, the needles for subcutaneous insulin injections were much thicker (a diameter of 27 gauge) and much longer (up to 16 mm in 1985) than those that constitute the current **gold standard** of reference (**4 mm long × 32 gauge thick**), developed in 2010 after a long trajectory of technological evolution [1]. Currently, there are even thinner and shorter needles on the market than these; however, they are supported by scientific evidence that is still in the preliminary stages [2,3].

The need to use shorter needles was already identified several years ago, highlighting a high risk (over 80% in non-obese children) of an unwanted intramuscular administration of insulin with needles measuring 12.7 mm in length [4]. Since then, research and manufacturing companies have engaged in the study of shorter needles, and 8 mm needles have proven effective in reducing unwanted intramuscular injections; however, these issues were still noted, especially in children, adolescents, and lean adults [5]. Even shorter needles were subsequently produced, and in comparison with 8 mm needles, 6 mm needles were shown to be more effective in reducing the risk of intramuscular injection (45% vs. 15%). Subsequent studies have shown that 5 mm needles are comparable to 8 mm needles in terms of metabolic control and patient preference and can be safely used even in obese diabetics [6]. Further studies showed that 4 mm long needles are effective in subcutaneous insulin delivery at all potential injection sites in diabetic adults. Particularly in an interesting randomized controlled study, Hirsch et al. demonstrated how injections with needles measuring 4 mm and 32 G guarantee glycemic control equivalent to those made using needles with 5 and 8 mm needles measuring 31 G thick, without any differences in terms of insulin dispersion, and were accompanied by less pain [7].

Many clinicians continue to use longer needles on obese patients, but well-established scientific evidence documents that such a choice is not justified. Recent studies have shown that there are no significant differences in glycemic control in obese patients using shorter needles, with over-lapping plasma levels of glycated hemoglobin comparing needles with 29 G and 12.7 mm in length compared to those with 31 G/6 mm or 31 G/5 mm compared to those with 31 G/8 mm [8,9]. Frid and Linde documented that there are no substantial differences in the uptake of insulin injected at different levels of subcutaneous depth, both in the abdomen and on the thighs [10]. No difference in the pharmacokinetics and pharmacodynamics of insulin has been demonstrated using needles with different lengths [11]. It is known that skin thickness differs negligibly between groups of patients of different ages, sexes, and ethnicities. Therefore, it can be assumed that the shortest needles (4 mm) can be used effectively on all individuals, ensuring the correct release of the drug into the subcutaneous adipose layer even in the presence of excess fat, as is the case in overweight and obese individuals, as the absorption of insulin is not affected by the level of subcutaneous depth into which it is injected. Therefore, the use of short needles (4–5 mm) is safe and burdened with fewer side effects (skin damage, intramuscular or intradermal injection) even in individuals with excess weight; it is also generally preferred by patients because it is associated with less tenderness (a better pain score) [12]. Since the thickness of the subcutaneous layer varies in relation to a number of factors, including race, age, gender, and BMI, as well as depending on the different parts of the body, the layer actually reached by the injection depends on the length of the needle used according to the injection technique and the features of the subject. During insulin therapy, accidental intradermal and intramuscular injections can increase pain and/or have a negative impact on glycemic control. The most suitable needle length for patients depends on skin thickness and the distance from the muscle fascia. In a recent study, the thicknesses of each subject's skin and subcutaneous fat were measured with an ultrasonic probe (7 to 12 MHz). Using variance analysis and multiple linear regression, the average skin thickness (ST) was 2.29 ± 0.37 mm in the abdomen and 2.00 ± 0.34 mm in the upper arms, while the average thickness of the subcutaneous fat (SCT) was 10.15 ± 6.54 mm in the abdomen and 5.50 ± 2.68 mm in the upper arms. This study has shown that the major factors influencing the thickness of the subcutaneous adipose layer of the abdomen and upper arms are gender and BMI [13]. It is, therefore, likely that in these locations, insulin will not be injected subcutaneously at any of the needle's lengths but that the risk of intramuscular injection will increase with longer insulin pen needles and a lower BMI, supporting the appropriateness of determining the length of insulin pen needles based on the thickness of the skin and subcutaneous fat both in the abdomen and in the upper arm, at least in patients with type 2 diabetes, which the cited study refers to. A layer of subcutaneous fat thicker than 35% was found in the women, and there was 22% less visceral fat in comparison with men. This indicates that in obese subjects, weight loss with the diet exposes them to differences in the thickness of the subcutaneous tissue, posing the problem that a relatively long needle, which was optimal before the diet, may lead to the insulin being injected intramuscularly after the diet, depending on their gender and part of the body. With age, the thickness of the deep fat layer is increased, whilst the increase in the body mass index mainly enlarges the thickness of the superficial layer. In that study of 150 type 2 diabetic patients undergoing insulin therapy, who were evenly distributed in terms of gender, age group, and BMI, the values of their gluteal subcutaneous thickness were assessed, giving the following gender-specific mathematical formulae: men [total thickness (in millimeters) = −33.56 + (age × 0.078) + (body mass index × 3.042)] and women [total thickness (in millimeters) = −56.997 + (age × 0.1) × (body mass index × 3.86)] [13]. The following values for the subcutaneous tissue thickness were obtained: A 55-year-old man and a BMI of 34 = 169.09 mm, a 40-year-old man and a BMI of 26 = 115.77 mm (a difference of 53.32 mm); a 55-year-old woman and a BMI of 34 = 193.7 mm, a 40-year-old woman and a BMI of 26 = 161.357 mm (a difference of 32.34 mm), with a substantial gender difference at the same age and BMI (women vs. men: +24.61 mm for the 55-year-old group and a BMI of 34 and +45.6 mm for the 40-year-old group and a BMI of 26). Some differences are evident in children with diabetes [14]. As shown by the above data, there are differences in subcutaneous thickness not only between genders (also depending on possible weight loss following a diet) but also within the same gender in relation to age and BMI [15]. In conclusion, the data available in the literature indicate overall that the risk of intramuscular injections can be considered greater in male subjects, especially those above pubertal age, and, within the same gender, in those at an older age with a lower BMI [6,16]. Multivariate analyses showed that parts of the body, gender, BMI, and race were statistically significant factors for ST variability, but the final effects were too small to have a clear impact on injection. However, by combining the ST and SCT (subcutaneous) measurements of all participants at the four injection sites and estimating the depth of drug delivery with variable-length needles inserted at both 90 and 45 degrees for the full length of the needle and without skin depression, it was calculated that the 5 mm needle would result in a subcutaneous injection in over 98% of cases when inserted perpendicularly. In contrast, with the same technique, the percentage of intramuscular injections would have risen above 5% with the 6 mm needle and above 15% with the 8 mm needle, reaching 45% of cases with the 12.7 mm needle, which would have posed a 21% risk even when inserted at 45 degrees (Table 1).

Table 1. Needle length and tissue depth of injection were calculated from ST and SCT measurements

Needle Length	**Insertion at 90°**			**Insertion at 45°**		
	ID	**SC**	**IM**	**ID**	**SC**	**IM**
4 mm	0	1203	5	94	1114	0
5 mm	0	1186	22	4	1201	3
6 mm	0	1139	69	0	1198	10
8 mm	0	1023	185	0	1158	50
12.7 mm	0	665	543	0	953	255

Key: ID intradermal, SC = subcutaneously, IM: intramuscular. Data are expressed in millimeters. To calculate the distance between the surface of the skin and the muscle fascia, paired measurements of the skin and subcutaneous tissue were taken, assuming 90° or 45° needle insertion without skin compression and estimating the anatomical location of the injection, which was not performed.In addition to the length, it is important to underline how other technical characteristics of the needles can significantly affect the comfort of the injection, influencing the ease of penetration of the needle into the skin and consequently the patient's acceptance and approval, such as the external caliber (G), sharpening, lubrication, and geometry of the needle tip. In a 2012 study comparing different needle sizes (32 G × 4 mm, 31 G × 5 mm, and 31 G × 8 mm) to 5 facets (5B) versus needles with equivalent sizes but with a 3-faceted tip (3B),, preclinical tests demonstrated a significant reduction in penetration strength (23%; $p \leq 0, 01$) with 5B vs. 3B tip needles. In a study [17], patients were blinded to the pen needle bevel designs. In that experiment at home, 810 injections were completed; about 2/3 of the subjects used the 5-bevel PN 5–10 times. After home use, 97.6% (95% lower confidence bound, 93.1%) of users found the 5-bevel acceptable, significantly higher than the 80% criterion. The 5-bevel pen needles were rated higher than usual pen needles for ease of insertion (63.1% vs. 7.1%), comfort (61.9% vs. 8.3%), and preference (60.7% vs. 10.7%), each $p < 0.01$. Also, the mean VAS score for pain was significantly lower for 5-bevel vs. usual 3-bevel pen needles (Table 2). The number of injections completed was not related to pain ($p = 0.99$).

This was associated with the finding of a significantly larger proportion of patients ($p < 0.01$) who reported a reduction in pain and a preference for 5B needles, supporting the evidence that a needle with innovative tip geometry can promote a better acceptance of injection therapy [17]. This paper clearly indicate that needle tip geometry affects penetration force and a 5-bevel needle tip is perceived as less painful and is preferred by subjects following home use for usual injections**.** Therefore, when choosing the best needle for the patient, besides the certified length, the geometry of the technologically innovative tip, which is equally certified, must be evaluated to ensure a lower penetration force into the skin, which in turn has a direct impact on the comfort of the injection, minimizing pain.

The external caliber of the needle, in particular, is related to the flow of the drug within the lumen and may also influence the delivery of the correct dose of insulin. In fact, the decrease in the external diameter of the needle (indicated by the increase in G) corresponds to a reduction in the internal diameter, which follows a greater resistance to the flow of insulin inside the cannula and a slowdown in the injection rate; this entails the need to apply greater force on the pen button, with the risk of causing irregular drug delivery and greater pain and discomfort for the patient [18]. For example, an extra-thin wall needle (ETW) with an outer diameter of 34 G will have a smaller internal diameter than an extra-thin wall needle with an external diameter of 32 G; this leads to a lower flow with the 34 G needle compared to the 32 G needle, and its use implies a longer insulin administration time as well as a greater resistance to the plunger; therefore, the injection takes longer and requires a greater force of penetration, ending up being more painful. To increase the flow, the latest generation needles with ultra-thin-wall technology ([UTW] according to ISO 9626:2016) have been developed and are to be preferred since, with the same external diameter (G), they are equipped with a larger internal diameter (Table 2), which allows for a greater flow of the drug and the possibility of applying a lower penetration force, ensuring advantages in terms of flow, tenderness, and ease of use. Based on these considerations, the largest internal diameter with the same external diameter (declared G) is a quality and technological innovation requirement of the needle [19].

In conclusion, the needle that represents the gold standard of high technological quality is the one that contains the following innovative features: 4 mm in length and an external diameter of 32 G, suitable for practically all types of patients; 5-faceted sharpening to ensure excellent penetration with less skin damage and less pain; ultra-thin walls, according to ISO 9626:2016, to ensure greater flow and therefore less force to be applied for injecting; equipped with tip lubrication, to facilitate penetration and reduce tenderness.

Table 2. Internal and external diameters of different needles

Metric Size (mm)	Gauge	OD_{min} (mm)	OD_{max} (mm)	Wall	ID_{min} (mm)
0.18	34	0.178	0.191	ETW	0.105
0.20	33	0.203	0.216	ETW	0.125
0.23	32	0.229	0.241	ETW	0.125
				UTW	0.146
0.25	31	0.254	0.267	ETW	0.146
				UTW	0.176

ETW extra-thin wall, UTW ultra-thin wall. The internal diameter of the 34 G ETW needle is lower than the internal diameter of the 32 G UTW.

Based on these considerations, the largest internal diameter with the same external diameter might be considered a quality and technological innovation regarding insulin needles.

The use of needles that comply with the high-quality gold standard, together with an educational program that ensures that the correct injection technique is widely disseminated, represents a more cost-effective option than the use of longer pen needles and without the support of any educational program, with it being able to represent an overall economic saving for the Italian National Health Service [20].

Insulin should be injected into the subcutaneous tissue and not into muscle tissue, as the latter leads to faster uptake and a higher risk of hypoglycemia.

Using a 4 mm needle, it should be injected at 90 degrees without any pinching, while with 6 mm needles or bigger, and particularly with insulin syringes, whose needle measures no less than 8 mm, insulin should be injected applying the pinch technique and sustained until the injection has been completed at an angle of 45 degrees. Even in children under the age of 6, or in particularly thin individuals, it is necessary to pinch and inject insulin perpendicularly into the skin fold and always use a 4 mm needle. The use of quality needles, together with the systematic rotation of the injection sites and the replacement of the needle for each administration, are essential to avoiding the formation of lipodystrophies, which are associated with a variable and unpredictable uptake of insulin and modify the pharmacokinetics and pharmacodynamics of the injected insulin. About half of patients worldwide use the same needles more than once. In most cases, multiple uses occur up to five times (or less), but up to 30% of people say they reuse the same needle six or more times (Table 3). Lipohypertrophy is more frequent in people who reuse needles, but reuse appears to be a less powerful predisposing factor than failure to rotate the injection site, use of limited injection areas, and prolonged insulin intake [21].

About half of patients worldwide use the same needles more than once; this practice is more widespread among those using pens compared to those using syringes, although in this regard, there is a huge difference between the various countries. There is also a large degree of variability in terms of the number of times the needle is reused: in most cases, multiple uses occur up to five times (or less), but up to 30% of people say they reuse the same needle six or more times (Table 3). Patients who use this practice report various reasons that push them in this direction, but comfort and economic savings are the preeminent motivations, especially for pen users.

Table 3. Reuse of needles by users of insulin pens and syringes .

	Pen Users (%)	**Syringe Users (%)**
Those reusing needles (pens, n = 11,961; syringes, n = 2711)		
Yes	55.8	38.8
No	44.2	61.2
Frequency of reuse (pens, n = 3985; syringes, n = 1126)		
Twice	30.7	35.4
3–5 times	39.7	44
6–10 times	16	11.4
>10 times	13.6	9.2
Reasons for reusing them (pens, n = 3891; syringes, n = 1117)		
I do not have another needle	9.2	14.5
To save Money	23.3	38.4
To avoid generating too much waste	6.8	6.6
For convenience	41.2	26.1

In a recent study, the full needle insertion–extraction cycle was examined as a quantitative descriptor of the whole injection experience on artificial skin equivalents. The authors demonstrate that 3-bevel needles do not have the same performance as those of 5-bevel needles, showing a lower capacity for drag and extraction, and may cause patients more pain [22]. Therefore, when choosing the best needle for the patient, besides the certified length, the geometry of the technologically innovative tip, which is equally certified, must be evaluated to ensure a lower penetration force into the skin, which in turn has a direct impact on the comfort of the injection, minimizing pain.

Lipohypertrophy is more frequent in people who reuse needles, but reuse appears to be a less powerful predisposing factor than failure to rotate the injection site, use of limited injection areas, and prolonged insulin intake [23]. In fact, in patients with type 1 diabetes, the rotation of injections over a large area and the use of fast and long-acting insulin analogs are known to be the most important and modifiable factors in minimizing insulin-related lipohypertrophy, while in a recent study, needle reuse and frequent injections have not contributed significantly to the development of lipohypertrophy [24,25].

At present, not enough scientific evidence is available to clearly attest to the danger of reusing needles for subcutaneous insulin injection, but this practice is very common among people with diabetes, so further studies are needed to establish its safety [26]. As far as we know, there is a correlation between the reuse of the same needle and the formation of areas of lipohypertrophy; in addition, the reuse of the needle is associated with pain and bleeding at the injection site, so the diabetes team should discourage this incorrect practice (test level 2, strength of recommendation A) [27,28]. In contrast, the use of the 4 mm needle is associated with a lower rate of lipohypertrophy than the 8 mm one. In addition, some data show that needle reuse may be associated with a more painful injection, and pain seems to increase depending on the number of times the needle is reused. Reuse may also be associated with unexplained hypoglycemia, glycemic variability, hyperglycemia, and slightly higher HbA1c levels, but not with insulin skin losses [29].

3. Physicological Support

Pain associated with injections is often a key component of needle phobia; working on this aspect to reduce the anxiety and stress experienced by the patient helps them feel understood and supported. Needle technology, thus, can also help in the presence of needle phobia by reducing pain.

A fear of needles, more commonly known as **needle phobia,** is an extremely widespread condition. A total of 10% of the global population suffers from the disorder, with more incidence among women, youngsters, those suffering from chronic diseases, and those with a lower level of education [30–32].

Diabetes forces insulin-treated patients to constantly keep their blood sugar levels under accurate control through a series of essential daily actions that are repeated multiple times per day and around which they must learn to build their lifestyle. For these patients, caring for diabetes involves a quantifiable commitment, which translates into 4 injections per day, which corresponds to 28 injections per week, or 112 injections per month, for a total of 1344 injections per year, without counting the pricks made to "correct" treatment and those made for measuring blood sugar levels. All of this corresponds to a total of around 72 uninterrupted annual hours spent injecting in order to treat the disease, which has a significant impact on quality of life in terms of the patient's time and emotional investment. Over time, the distress experienced in carrying out these actions can lead to patients viewing blood sugar monitoring and insulin injections as a massive inconvenience and emotional burden, making them feel vulnerable to the exacerbation of anxious and phobic responses. Fear and an aversion to needles, albeit without an actual phobia, can hinder the diabetic patient's adherence to treatment, leading them not to monitor their blood sugar levels or even to lower the amount of insulin they inject or the number of injections required, with the outcome being that control over the disease is worsened. In order to avoid these consequences, needle phobia must be identified in advance by way of an accurate medical history and appropriately dealt with through either physical or psychological treatments [33–35]. If the diagnostic criteria for the specific phobia are observed, needle phobia can be treated with structured psychotherapy sessions and resorting to different techniques, which include systematic desensitization and gradual exposure of a cognitive and behavioral origin, that have proven to be effective. Sub-threshold disorders can be treated by nurses through the use of caring approaches. For example, several studies have shown the importance of injecting in a calm environment, whereby the patient can lie down to reduce the risk of a vasovagal crisis, feel safer when handling their own anxiety, and have the time needed to recover. In these cases, a good communicative approach is fundamentally important; in fact, actions such as calming the patient down and accommodating their fears empathetically can be of therapeutic value in that if they are reassured, they feel more relaxed [36–40]. The pain associated with injecting is often a key component of needle phobia, and working on this aspect so as to lower the anxiety and stress it causes can be powerful. The pain-free technique involves a series of procedures that make injecting both subcutaneously and intramuscularly less painful. The main fundamentals of this technique involve using soft needles, which are inserted quickly yet delicately (soft touch), slowly injecting the drug at a constant speed, and heating it up prior to injecting it. However, this is not applicable to the new types of insulin, which must be used at room temperature. Learning principles that the patient can implement themselves also has the advantage of increasing their sense of control over the disease. Teaching the pain-free technique requires a comfortable setting, sufficient time, and the availability of the healthcare worker to talk to the patient about the origin of their fears, offering them reassurance and psychological support [41]. Nowadays, the technology available for treating diabetes may also be of use when it comes to needle phobia, offering patients different alternatives to traditional injecting practices. For example, using medical devices such as subcutaneous implantable cannulas (e.g., the i-PORT that can stay in position for a maximum of 3 days) ensures multiple administrations of insulin and reduces the number of pricks needed. Another option could be to use short needles equipped with ultra-thin walls, which, besides having less impact visually, are also less painful. Likewise, "covered" needles, such as those defined as safety needles, can be used; this could be extremely useful as these devices have the double advantage of preventing accidental pricks and hiding the needle, which could help to reduce fear in those suffering from needle phobia.

4. Educational Support

Certainly, the educational aspects are no less important in the correct management of insulin needles. The best technology cannot be used if you do not know how to use it. ***Drugs do not work in patients who do not take them."*** An aphorism as simple as it is indisputable for the truth that it expresses and that nevertheless should continue "as well as in those who do not take them well," considering that adherence to treatment and a correct administration contribute decisively to the success of medical therapies. In a healthcare system, education must be focused on the person, and educational activities must be adapted to people's personal, professional, and cultural needs. From websites, through telemedicine, apps for different devices, and global operating systems, to pharmacies and volunteer associations, people can access educational programs faster and more conveniently. Technology has shown that it can offer a valuable contribution to the patient's educational path and effective support for the self-management of insulin therapy, with the clear intention of facilitating the self-management of diabetes and, subsequently, improving the quality of life of the patients themselves [42,43]. The multi-professional and multidisciplinary approach to education and the extension of its application to non-traditional settings lead to the involvement of new and different healthcare and non-healthcare roles, who can obtain the certification of educational skills at different levels with the right training. For example, there is increasing evidence on the effectiveness of diabetes education and support for diabetes self-management, including, in the long term, community-based training programs by health professionals trained in relation to improving lifestyle and glycemic control [44,45].

A significant educational contribution also comes from patient associations based on volunteering, which represent an important link between the health system, people with diabetes, relatives, and society, and for this reason, they are present in diabetes services [46–48]. Therefore, today, a real educational role is bestowed on the so-called "equal trainers" or "diabetic guides," that is, appropriately trained diabetic patients who become mediators of peer education through the transfer of information to other people with the same disease or even to figures such as "lay leaders," who ensure continuous support even outside the health context [49,50]. There is evidence from the ISTERP-3 Study that well-conducted structured educational plans, not limited to the first visit, can achieve better clinical outcomes and less burden [51,52].

Within healthcare technologies, the assignment of insulin therapy represents one of the most complex aspects due to the patient's perceived experience and aspects related to the efficacy and safety of the type of care. In order to begin insulin therapy, a device must be chosen where there is a lower probability that the treatment will be interrupted at the beginning and in the long term. They are preferable on account of greater precision and less variability in terms of doses and are associated with cost savings in both the short term, for example, reducing the amount of insulin that would be wasted using a vial, and in the long term, due to a relatively lower risk of hypoglycemia. Less hypoglycemia in hospitals significantly reduces acute myocardial and stroke complications [53–56], as it does in the outpatient setting, where the use of pens is linked to a lower number of emergency hospital visits [57,58]. When insulin therapy must be started in the hospital, it is important that it begins with pens and that the patient is immediately instructed in the use of needles. Educating about insulin therapy must, therefore, begin in the hospital, where the patient has the actual chance to observe how to implement the correct technique with the help of expert healthcare personnel, to ask questions if they have any doubts, and to be directed to using the most suitable medical devices to resolve any individual peculiarities. The nursing dedicated to the patient and their caregiver, if any, is considered a fundamental part of the pathway for the use of insulin therapy by means of a pen-based device in hospitals. Care must be taken to educate on the correct use of needles [59].

Particular Cases

(A) Subcutaneous tissue is unexpectedly thin

In very young children (<6 years), even short needles used without skin folds may be associated with a significant amount of inappropriate intramuscular injections, equal to 20.2% with 4 mm needles, double with 5 mm needles, and triple with 6 mm needles [6]. Therefore, in order to reduce intramuscular injections and avoid the resulting increased variability in blood sugar, even in the absence of EBM, the use of short needles (4 and possibly 3.5 mm) is recommended in all pediatric patients, inserting the needle perpendicularly into a skin fold in children age <6, or at 45° if the fold is not easy to make [23].

(B) Cellulite in older age

Cellulite can be understood as an imbalance between the restraining and extrusion forces at the subcutaneous junction; older women with a high body mass index have the highest risk of developing (or worsening) cellulite, which is another confounding factor for subcutaneous insulin injections, as insulin uptake is more variable at the sites affected by cellulite [60]. Thus, particularly in women, there may be differences in insulin uptake into the subcutaneous tissue depending on the appearance and extent of cellulite due to age. In the elderly, insulin therapy with long needles carries an increased risk of intramuscular injection, as the subcutaneous panniculus adiposus generally thins with age. Moreover, in this population, the increased rate of insulin uptake following intramuscular injection can cause particularly devastating and life-threatening hypoglycemic crises since they are triggered by the frailty typical of old age (geriatric syndrome), which various comorbidities contribute to [61]. Therefore, for the reasons outlined above, the use of short needles (4 mm) is recommended in this category of patients in order to ensure the adoption of a single injection technique at a right angle, without skin folds [7].

(C) Resistance to insulin administered subcutaneously and intramuscularly

Even when the right needle is used in the right way, an insulin injection may be ineffective. Such is the way of the so-called "type 1 diabetes mellitus with resistance to insulin administered subcutaneously and intramuscularly (DRIASM)." This is a rare condition that consists of insulin resistance subcutaneously and intramuscularly and normal or near-normal sensitivity intravenously. The way to overcome this situation was usually intravenous continuous insulin injection or pancreas transplant; both situations were difficult to manage. One way to overcome this situation is to use a continuous intraperitoneal insulin infusion (CIPII). This method has been applied with subcutaneous insulin pumps delivering insulin directly in the peritoneum [62] or by the use of external pumps connected through a port to the peritoneal space (DiaPort) crossing the skin to the peritoneum [63]. We also had experience with these devices, and this method is only applicable to those people since management of the port is rather complex and the patient needs a surgical intervention for either the subcutaneous pump or the DiaPort system [64].

5. Conclusions

Patient quality of life is universally recognized as a fundamental objective of healthcare, although its assessment has not yet fully entered into clinical practice. In an illness such as diabetes, which is becoming more and more widespread, the dimension of quality of life takes on a particularly important role. This is not only because of the chronic nature and severity of the disease and its possible complications, which can dramatically affect the well-being of the individual, but also due to the heavy burden that the diabetic patient must face every day in order to manage the disease. This has a significant and constant effect on the patient's entire existence, deeply affecting their psychophysical state and their perception of their general health. Therefore, especially when it comes to diabetic patients, quality of life must be considered a fundamental indicator for assessing the results of medical treatment and must constitute the unitary approach on which to base the entire clinical management. For a large proportion of diabetic patients, insulin therapy is an indispensable treatment, and the aspects related to the management of the injection practice have a heavy impact on their daily lives, on their relational and social dimensions, and on their subjective well-being. This document provides indications for a global quality approach to the management of insulin injection therapy, focusing on the quality of life of the diabetic patient so that all care choices are based on a better balance between the pursuit of therapeutic objectives and attention to aspects relevant to the patient and their overall well-being. To this end, the recommendations provided in this document, which are addressed to all professionals involved in the management of diabetic patients, examine the various areas of insulin injection therapy, interpreting the concept of quality within each of them and adopting a 360° view, thanks to the different points of view of a multidisciplinary panel of experts with diverse skill sets. In this context, offering quality care to diabetic patients, in addition to choosing the best treatments, reduces complications and disabilities resulting from the disease. This includes more empathetic communication with the patient in order to encourage the acceptance of insulin therapy, greater commitment to preventing the local complications of injection therapy, acceptance of the patient's personal expectations and attitudes, attention to emotional aspects, and support for psychological problems (for example, in the case of needle phobia). It also involves considering factors that hinder acceptance of the therapy (such as discomfort and pain related to injection) and the patient's active involvement in the therapeutic management of the disease through education, empowerment, and quality technology. In insulin therapy, the choice of high-tech pen needles is crucial not only to ensure proper injection technique and optimal drug intake, which are essential for effective therapy, but also to promote patient comfort and the least traumatic user experience possible, which are crucial to ensuring the adherence to therapy necessary to achieve treatment goals and the persistence in treatment that is essential in order to reduce long-term complications. Technologically innovative insulin pen needles can prevent local therapy complications, such as lipodystrophies [65], and ensure safety for the user and the healthcare worker or caregiver by preventing accidental needle pricking. Overall, the use of quality needles can lead to a reduction in healthcare expenditure due to the cost savings associated with quality care that improves the clinical outcome of diabetic patients, reducing short- and long-term complications and the costs of managing them. According to the literature, the innovative characteristics of the insulin pen needle that identify the gold standard of high technological quality are its 4 mm length and 32 G external diameter with an ultra-thin wall. These characteristics ensure advantages in terms of flow and tenderness. To ensure optimal inoculation in all types of patients, innovative tip geometry with five bevels is used to ensure optimal penetration with less skin damage and less pain. The tip is sharpened and lubricated to facilitate insertion and reduce pain. Thin-wall technology (extra- and ultra-thin walls) ensures adequate flow and, therefore, less force to be applied for the injection. Additionally, double-protection safety mechanisms for both tips prevent accidental pricking during use and disposal (safety needles). In technical specifications, the quality requirements for insulin pen needles must be extended to the services related to the provision of insulin needles, including training for healthcare professionals, educational projects for patients aimed at promoting empowerment and disseminating validated information on proper injection techniques and avoidance practices (such as the non-rotation of sites, multiple needle use, and promiscuous use of insulin pens), and digital tools such as mobile digital apps certified as diabetes medical devices aimed at optimizing treatment and facilitating patient self-management of therapy. A concise summary of recommendations is given below; more extensive material can be found in the attached Appendix A.

Author Contributions: All authors participated in the preparation of the manuscript. Everyone independently collected a bibliography on the various topics proposed (technology, psychological aspects of the puncture, and educational aspects). The outline of the work was drawn up after numerous meetings, both face-to-face and via the web, to decide on the writing line. The first draft of the work was prepared by G.T., A.D., and M.A.T., and then each author subsequently made modifications and changes. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Conflicts of Interest: No conflicts of interest exist for any of the authors regarding this manuscript.

Appendix A

Summary of recommendations

SUBJECT	FOCAL POINTS
FALSE BELIEFS	
In some situations, the small needles are unable to reach the correct area of administration.	The 4 mm needle, which is inserted at a 90° angle, is considered the best one in that it reaches the correct layer for administering insulin in practically all types of diabetic patients.
PSYCHOLOGICAL ASPECTS AND NEEDLE PHOBIA	
Diagnosis of needle phobia	The diabetes team should pay attention to the diagnosis of needle phobia with a view to improving the patient's quality of life and avoiding poor adherence to injection therapy. The diagnosis requires an in-depth psychological interview with the patient.
EDUCATING THE DIABETIC PATIENT	
Educational therapy	The training aimed at boosting the patient's empowerment and their knowledge of managing the treatment themselves must be considered an integral part of the treatment of diabetes in the long term and an essential tool for improving the patient's quality of life, which constitutes one of the therapeutic responsibilities of the care team.
Establishment of a multi-professional diabetes team:	In settings with acute and critical patients, the establishment of a multi-professional diabetes team in the II-level hub hospitals of the regional hospital network and a PDTA in the spoke hospitals is preferable.
Protagonists in the multi-professional diabetes team	The team should include a diabetes doctor, a specialist nurse, a nutritionist, a pharmacist, and a psychologist.
Other trainers	The "equal trainers" or "diabetic guides," which are diabetic patients who become mediators of peer education for other people with the same disease, can be considered real educators if they are suitably trained.
INSULIN NEEDLE TECHNOLOGY	
The length and thickness of the needle are the most important feature	The geometry and sharpening of the tip, the internal lumen, and the flow and lubrication of the needle must also be considered.
I. Length:	4–5 mm needles are preferred for most patients, with the same G (gauge), and they have no differences in pharmacokinetics and pharmacodynamics compared to needles longer than 6–8 mm. In addition, they do not expose the user to the risk of intramuscular injections, skin damage, or pain.
II. Tip geometry and sharpening	With the same gauge and length, needles with 5-faceted *sharpening* (5B) are preferred over 3-faceted ones (3B) for better penetration (reduction in strength), less pain, and less bleeding (reduction in skin damage).
III. External needle caliber	Should be carefully evaluated. Smaller external diameters with the same wall lead to a reduction in

	flow and a consequent increase in the force to be applied to the pen button, causing greater pain and discomfort for the patient. The largest internal diameter with the same external diameter (declared G) is a quality and technological innovation requirement of the needle.
IV. Gold standard:	4 mm × 32 G needles, with 5-faceted sharpening and ultra-thin wall walls (for greater patient acceptance and better adherence to therapy), equipped with tip lubrication to facilitate penetration and reduce tenderness.
Safety	In order to prevent accidental pricking by the user and/or their caregiver, safety needles and syringes, i.e., those equipped with safety systems, needles with automatic double protection screens (on both ends of the needle), should be used.
SPECIAL TYPES OF PATIENTS	
Obese patients	In obese patients, shorter needles (4–5 mm) with a 90° injection technique with no folding are as effective as longer needles in maintaining good glycemic control, cause no adverse effects, and are preferred by patients.
Elderly patients	Short needles (4–5 mm) are recommended, which involve an easier injection technique (90° and without folding the skin); in fact, the subcutaneous panniculus adiposus generally thins with age, and long needles increase the risk of intramuscular lesions and severe hypoglycemic crises.
Extremely thin patients, those suffering from tremors or physical impairment	(Incapable of injecting at a 90° angle): choosing 5 mm needles and inoculating perpendicularly into the skin fold is useful.
Pediatric patients:	In very young children (≤6 years old), the skin folding technique should be used with a short (3.5–4.5 mm), ultra- or extra-thin needle for more flow and less resistance to the injection; older children can use 4.5 mm needles at a 90° angle technique.

References

1. Aronson, R.; Bailey, T.; Hirsch, L.; Saltiel-Berzin, R. Advances in insulin injection research influences patient adherence. *US Endocrinol.* **2013**, *9*, 114.
2. De Berardis, G.; Scardapane, M.; Lucisano, G.; Abbruzzese, S.; Bossi, A.C.; Cipponeri, E.; Nicolucci, A. Efficacy, safety and acceptability of the new pen needle 34G × 3.5 mm: A cross-over randomized non-inferiority trial; AGO 02 study. *Curr. Med. Res. Opin.* **2018**, *34*, 1699–1704.
3. Valentini, M.; Scardapane, M.; Bondanini, F.; Bossi, A.; Colatrella, A.; Girelli, A.; Nicolucci, A. Efficacy, safety and acceptability of the new pen needle 33G × 4 mm. AGO 01 study. *Curr. Med. Res. Opin.* **2015**, *31*, 487–492.
4. Polak, M.; Beregszaszi, M.; Belarbi, N.; Benali, K.; Hassan, M.; Czernichow, P.; Tubiana-Rufi, N. Subcutaneous or intra- muscular injections of insulin in children. Are we injecting where we think we are? *Diabetes Care* **1996**, *19*, 1434–1436.
5. Tubiana-Rufi, N.; Belarbi, N.; Du Pasquier-Fediaevsky, L.; Polak, M.; Kakou, B.; Leridon, L.; Hassan, M.; Czernichow, P. Short needles (8 mm) reduce the risk of intramuscular injections in children with type 1 diabetes. *Diabetes Care* **1999**, *22*, 1621–1625.
6. Kreugel, G.; Keers, J.C.; Kerstens, M.N.; Wolffenbuttel, B.H. Randomized trial on the influence of the length of two insulin pen needles on glycemic control and patient preference in obese patients with diabetes. *Diabetes Technol. Ther.* **2011**, *13*, 737–741.

7. Hirsch, L.J.; Gibney, M.A.; Albanese, J.; Qu, S.; Kassler-Taub, K.; Klaff, L.J.; Bailey, T.S. Comparative glycemic control, safety and patient ratings for a new 4 mm × 32G insulin pen needle in adults with diabetes. *Curr. Med. Res. Opin.* **2010**, *26*, 1531–1541.
8. Schwartz, S.; Hassman, D.; Shelmet, J.; Sievers, R.; Weinstein, R.; Liang, J.; Lyness, W. A multicenter, open-la- bel, randomized, two-period crossover trial comparing glycemic control, satisfaction, and preference achieved with a 31 gauge × 6 mm needle versus a 29 gauge × 12.7 mm needle in obese patients with diabetes mellitus. *Clin. Ther.* **2004**, *26*, 1663–1678.
9. Berard, L.; Cameron, B.; Woo, V. Pen needle preference in a population of Canadians with diabetes: Results from a recent patient survey. *Can. J. Diabetes* **2015**, *39*, 206–209.
10. Frid, A.; Linde, B. Intraregional differences in the absorption of unmodified insulin from the abdominal wall. *Diabet. Med.* **1992**, *9*, 236–239.
11. Hirose, T.; Ogihara, T.; Tozaka, S.; Kanderian, S.; Watada, H. Identification and comparison of insulin pharmacokinetics injected with a new 4-mm needle vs 6- and 8-mm needles accounting for endogenous insulin and C-peptide secretion kinetics in non-diabetic adult males. *J. Diabetes Investig.* **2013**, *4*, 287–296.
12. Hirsch, L.J.; Gibney, M.A.; Li, L.; Bérubé, J. Glycemic control, reported pain and leakage with a 4 mm × 32 G pen needle in obese and non-obese adults with diabetes: A post hoc analysis. *Curr. Med. Res. Opin.* **2012**, *28*, 1305–1311.
13. Frank, K.; Casabona, G.; Gotkin, R.H.; Kaye, K.O.; Lorenc, P.Z.; Schenck, T.L.; Lachman, N.; Green, J.B.; Duran-Vega, H.; Cotofana, S. Influence of Age, Sex, and Body Mass Index on the Thickness of the Gluteal Subcutaneous Fat: Implications for Safe Buttock Augmentation Procedures. *Plast. Reconstr. Surg.* **2019**, *144*, 83–92.
14. Lo Presti, D.; Ingegnosi, C.; Strauss, K. Skin and subcutaneous thickness at injecting sites in children with diabetes: Ultrasound findings and recommendations for giving injection. *Pediatr. Diabetes* **2012**, *13*, 525–533.
15. Ludescher, B.; Rommel, M.; Willmer, T.; Fritsche, A.; Schick, F.; Machann, J. Subcutaneous adipose tissue thickness in adults: Correlation with BMI and recommendations for pen needle lengths for subcutaneous self-injection. *Clin. Endocrinol.* **2011**, *75*, 786–790.
16. Hirsch, L.; Byron, K.; Gibney, M. Intramuscular risk at insulin injection sites—Measurement of the distance from skin to muscle and rationale for shorter-length needles for subcutaneous insulin therapy. *Diabetes Technol. Ther.* **2014**, *16*, 867–873.
17. Hirsch, L.; Gibney, M.; Berube, J.; Manocchio, J. Impact of a modified needle tip geometry on penetration force as well as acceptabil- ity, preference, and perceived pain in subjects with diabetes. *J. Diabetes Sci. Technol.* **2012**, *6*, 328–335.
18. Frid, A.H.; Kreugel, G.; Grassi, G.; Halimi, S.; Hicks, D.; Hirsch, L.J.; Strauss, K.W. New insulin delivery recommendations. *Mayo Clin. Proc.* **2016**, *91*, 1231–1255.
19. Bruttomesso D, Bossi AC, De Pascale A, Gruden G, Lauro D, Leonetti F, Mannucci E, Miccoli R, Natalicchio A, Perseghin G.; et al. Gli aghi per penna Insulina e altri anti-iperglicemici iniettivi. *Italian Diabetology Society Document*. https://www.siditalia.it/clinica/linee-guida-societari/send/80-linee-guida-documenti-societari/4056-2018-gli-aghi-per-penna-insulina-e-altri-anti-iperglicemici-iniettivi (Accessed on 20 March 2024)
20. Ravasio, R.; Grassi, G. The economic impact of the correct insulin injection technique associated with the use of 4 mm 32G needles in the treatment of patients with type 2 diabetes. *Glob. Reg. Health Technol. Assess.* **2018**, *2018*, 1–8.
21. Bahendeka, S.; Kaushik, R.; Swai, A.B.; Otieno, F.; Bajaj, S.; Kalra, S.; Karigire, C. EADSG Guidelines: Insulin storage and optimisation of injection technique in diabetes management. *Diabetes Ther.* **2019**, *10*, 341–366.
22. Documento di Consenso su Gestione e Utilizzo dei Sistemi Iniettivi dell'insulina in Ospedale. A cura del Gruppo Inter-Societario AMD-OSDI sulle Tecniche Iniettive. *Il Giornale di AMD* **2015**, *18*, 4–20.
23. Documento di Consenso sul Recepimento Italiano del Forum for Injection Technique and Therapy Expert Recommendations 2015. Update and additions by the AMD-OSDI inter-company group on injection techniques (16.05.2017). Recommendations for correct insulin administration, self-administration and injections in protected environments. https://aemmedi.it/wp-content/uploads/2016/09/FITTER2017.pdf (Accessed on 20 March2024)
24. Silver, B.; Ramaiya, K.; Andrew, S.B.; Fredrick, O.; Bajaj, S.; Kalra, S.; Makhoba, A. EADSG Guidelines: Insulin Therapy in Diabetes. *Diabetes Ther.* **2018**, *9*, 449–492.
25. Position statement OSDI 2011/2012 Somministrazione di insulina: Aspetti tecnici ed educativi, A.M.D.-S.I.D. Standard italiani per la cura del diabete mellito 2018. https://www.osdi.it/Uploads/Raccomandazioni/Raccomandazioni_01.pdf (Accessed on 20 March 2024)
26. Perfetti, R. Reusable and disposable insulin pens for the treatment of diabetes: Understanding the global differences in user preference and an evaluation of inpatient insulin pen use. *Diabetes Technol. Ther.* **2010**, *12* (Suppl. 1), S79–S85.
27. Frid, A.H.; Hirsch, L.J.; Menchior, A.R.; Morel, D.R.; Strauss, K.W. Worldwide Injection Technique Questionnaire Study: Population Parameters and Injection Practices. *Mayo Clin. Proc.* **2016**, *91*, 1212–1223.
28. Barola, A.; Tiwari, P.; Bhansali, A.; Grover, S.; Dayal, D. Insulin-related lipohypertrophy: Lipogenic action or tissue trauma? *Front. Endocrinol.* **2018**, *9*, 638.
29. Zabaleta-del-Olmo, E.; Vlacho, B.; Jodar-Fernandez, L.; Urpi-Fernandez, A.M.; Lumillo-Gutierrez, I.; Agudo-Ugena, J.; Violán, C. Safety of the reuse of needles for subcutaneous insulin injection: A systematic review and meta-analysis. *Int. J. Nurs. Stud.* **2016**, *60*, 121–132.
30. Wright, S.; Yelland, M.; Heathcote, K.; Ng, S.K. Fear of needle nature and prevalence in general practice. *Aust. Fam. Physician* **2009**, *38*, 172–176.

31. Kose, S.; Mandiracioglu, A. Fear of blood/injection in healthy and unhealthy adults admitted to a teaching hospital. *Int. J. Clin. Pract.* **2007**, *61*, 453–457.
32. Cox, A.C.; Fallowfield, L. After going through chemotherapy I can't see another needle. *Eur. J. Oncol. Nurs.* **2007**, *11*, 43–48.
33. Emanuelson, J. The Prevalence of Needle Phobia. Available online: www.needlephobia.com/prevalence.html (accessed on 23 April 2024)).
34. American Psychiatric Association. *DSM-5. Manuale Diagnostico e Statistico dei Disturbi Mentali*; Raffaello Cortina: Milano, Italy, 2014.
35. Alonso, J.; Angermeyer, M.C.; Bernert, S. Prevalence of mental disorders in Europe results from the European Study of the Epidemiology of Mental doisoerders. *Acta Psychiatr. Scand. Supll.* **2004**, *420*, 21–27.
36. Sokolowski, C.J.; Giovannitti, J.A., Jr.; Boynes, S.G. Needle phobia: Etiology, adverse consequences, and patient management. *Dent. Clin. N. Am.* **2010**, *54*, 731–744.
37. Girardi, M. Perché si ha Paura Degli Aghi? La Risposta Non è Così Scontata, 23/08/2020. Available online: www.ilgiornale.it/news/salute/ belonefobia-perch-si-ha-paura-degli-aghi-1885142.html (accessed on 23 April 2024).
38. Lynn, K. Needle phobics: Stuck on not getting stuck. *MLO Med Lab Obs* 2010, 42:46-8. demiology of Mental Disorders (ESEMeD) project. *Acta Psychiatr Scand Suppl* 2004, (420):21-7.
39. Zambanini, A.; Feher, M.D. Needle phobia in type 1 diabetes mellitus. *Diabet. Med.* **1997**, *14*, 321–323.
40. Goodspeed, R.B.; Lee, B.Y. What if… a patient is highly fearful of needles? *J. Ambul. Care Manag.* **2011**, *34*, 203–204.
41. Mackereth, P.; Hackman, E.; Tomlinson, L.; Manifold, J.; Orrett, L. "Needle with ease": Rapid stress management techniques. *Br. J. Nurs.* **2012**, *21*, S18–S22.
42. Nikitara, M.; Constantinou, C.S.; Andreou, E.; Diomidous, M. The role of nurses and the facilitators and barriers in diabetes care: A mixed methods systematic literature review. *Behav. Sci.* **2019**, *9*, 61.
43. Greenwood, D.A.; Gee, P.M.; Fatkin, K.J.; Peeples, M. A systematic review of reviews evaluating technology enabled diabetes self-management education and support. *J. Diabetes Sci. Technol.* **2017**, *11*, 1015–1027.
44. Phillip, M.; Bergenstal, R.M.; Close, K.L.; Danne, T.; Garg, S.K.; Heinemann, L.; Hirsch, I.B.; Kovatchev, B.P.; Laffel, L.M.; Mohan, V.; et al. The Digital/Virtual Diabetes Clinic: The Future Is Now-Recommendations from an International Panel on Diabetes Digital Technologies Introduction. *Diabetes Technol. Ther.* **2021**, *23*, 146–154.
45. Spencer, M.S.; Kieffer, E.C.; Sinco, B.; Piatt, G.; Palmisano, G.; Hawkins, J.; Heisler, M. Outcomes at 18th months from a community health worker and peer leader diabetes self-management program for Latino adults. *Diabetes Care* **2018**, *41*, 1414–1422.
46. Foster, G.; Taylor, S.J.C.; Eldridge, S.E.; Ramsay, J.; Griffiths, C.J. Self-management education programmes by lay leaders for people with chronic conditions. *Cochrane Database Syst. Rev.* **2007**, *4*, CD005108.
47. American Association of Diabetes Educators. Teaching Injection Technique to People with Diabetes. *American Association of Diabetes Educators* 2017. Available online: https://www.adces.org/docs/default-source/practice/practice-documents/practice-papers/teaching-injection-technique-to-people-with-diabetes.pdf?sfvrsn=0 (accessed on 9 January 2024).
48. Therapeutic Patient Education. *Continuing Education Programmes for Health Care Providers in the Field of Prevention of Chronic Diseases*; Report of a WHO Working Group; WHO: Geneva, Switzerland, 1998.
49. Jansa, M.; Vidal, M. Therapeutic education in chronic patients: The diabetes model. *Endocrin. Nutr.* **2015**, *62*, 53–55.
50. Tattersall, R.L. The expert patient: A new approach to chronic disease management for the twenty-first century. *Clin. Med.* **2002**, *2*, 227–229.
51. Gentile, S.; Guarino, G.; Della Corte, T.; Marino, G.; Satta, E.; Pasquarella, M.; Romano, C.; Alfrone, C.; Giordano, L.; Loiacono, F.; et al. The Economic Burden of Insulin Injection-Induced Lipohypertophy. Role of Education: The ISTERP-3 Study. *Adv. Ther.* **2022**, *39*, 2192–2207.
52. Gentile, S.; Guarino, G.; Corte, T.D.; Marino, G.; Fusco, A.; Corigliano, G.; AMD-OSDI Study Group on Injection Techniques and Nefrocenter Research; Nyx Start-up Study Group. Insulin-induced skin lipohypertrophy in type 2 diabetes: A multicenter regional survey in Southern Italy. *Adv. Ther.* **2022**, *39*, 2192–2207.
53. Clement, S.; Braithwaite, S.S.; Magee, M.F.; Ahmann, A.; Smith, E.P.; Schafer, R.G.; Hirsch, I.B.; on behalf of the Diabetes in Hospitals Writing Committee. Management of Diabetes and Hyperglycemia in Hospitals. *Diabetes Care* **2004**, *27*, 553–591.
54. Capes, S.E.; Hunt, D.; Malmberg, K.; Gerstein, H.C. Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: A systematic overview. *Lancet* **2000**, *355*, 773–778.
55. Capes, S.E.; Hunt, D.; Malmberg, K.; Pathak, P.; Gerstein, H.C. Stress hyperglycemia and prognosis of stroke in nondiabetic and diabetic patients: A systematic overview. *Stroke* **2001**, *32*, 2426–2432.
56. Candelise, L.; Landi, G.; Orazio, E.N.; Boccardi, E. Prognostic significance of hyperglycemia in acute stroke. *Arch. Neurol.* **1985**, *42*, 661–663.
57. Davis, E.M.; Christensen, C.M.; Nystrom, K.K.; Foral, P.A.; Destache, C. Patient satisfaction and costs associated with insulin administered by pen device or syringe during hospitalization. *Am. J. Health Syst. Pharm.* **2008**, *65*, 1347–1357.
58. Miao, R.; Wei, W.; Lin, J.; Xie, L.; Baser, O. Does Device Make Any Difference? A Real-world Retrospective Study of Insulin Treatment Among Elderly Patients With Type 2 Diabetes. *J. Diabetes Sci. Technol.* **2014**, *8*, 150–158.
59. Buysman, E.; Conner, C.; Aagren, M.; Bouchard, J.; Liu, F. Adherence and persistence to a regimen of basal insulin in a prefilled pen compared to vial/syringe in insulin-naıve patients with type 2 diabetes. *Adv. Ther.* **2015**, *32*, 1206–1221.

60. Rudolph, C.; Hladik, C.; Hamade, H.; Frank, K.; Kaminer, M.S.; Hexsel, D.; Cotofana, S. Structural gender dimorphism and the biomechanics of the gluteal subcutaneous tissue: Implications for the pathophysiology of cellulite. *Plast. Reconstr. Surg.* **2019**, *143*, 1077–1086.
61. Kim, K.S.; Kim, S.K.; Sung, K.M.; Cho, Y.W.; Park, S.W. Management of type 2 diabetes mellitus in older adults. *Diabetes Metab. J.* **2012**, *36*, 336–344.
62. Spaan, N.; Teplova, A.; Stam, G.; Spaan, J.; Lucas, C. Systematic review: Continuous intraperitoneal insulin infusion with implantable insulin pumps for diabetes mellitus. *Acta Diabetol.* **2014**, *51*, 339–351. https://doi.org/10.1007/s00592-014-0557-3.
63 Rieger, C.; Kurz, K.; Mueller-Hoffmann, W.; Gehr, B.; Liebl, A. New Design of a Percutaneous Port System for Continuous Intraperitoneal Insulin Infusion. *J. Diabetes Sci. Technol.* **2019**, *13*, 1158–1160. https://doi.org/10.1177/1932296819855425.
64, Pasquini, S.; Da Prato, G.; Tonolo, G.; Bonora, E.; Trombetta, M. Continuous intraperitoneal insulin infusion: An alternative route for insulin delivery in type 1 diabetes. *Acta Diabetol.* **2020**, *57*, 101–104. https://doi.org/10.1007/s00592-019-01398-3.
65. Campinos, C.; Le Floch, J.-P.; Petit, C.; Penfornis, A.; Winiszewski, P.; Bordier, L.; Lepage, M.; Fermon, C.; Louis, J.; Almain, C.; et al. An Effective Intervention for Diabetic Lipohypertrophy: Results of a Randomized, Controlled, Prospective Multicenter Study in France. *Diabetes Technol. Ther.* **2017**, *19*, 623–632.