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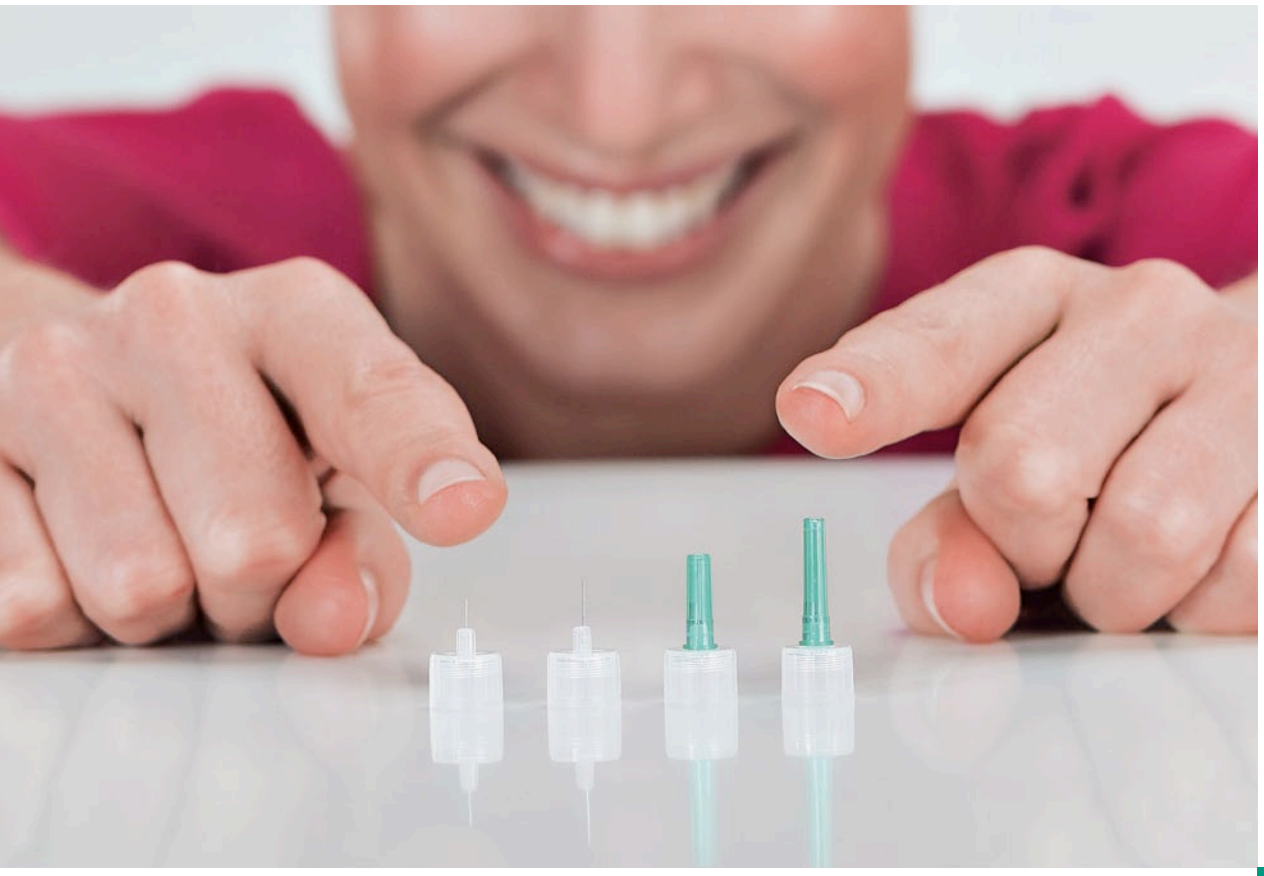
SHARING EXPERTISE



Insulin injection
with pen needles

CLINICAL EVIDENCE FOLDER

The Advantages of Short Pen Needles

1. INTRODUCTION

Diabetes mellitus is a major health problem that has become a global epidemic, especially in modern Western and Asian countries. The prevalence of type 2 diabetes mellitus is increasing because of the growing number of overweight and obese individuals. Recent studies have shown that 30 % of all diabetic patients are treated with insulin. [Hauner et al. 2007]

For patients and healthcare professionals, effective diabetes mangement is essential for successful therapy. The insulin injection technique has a significant effect on glycemic control, safety and tolerability.

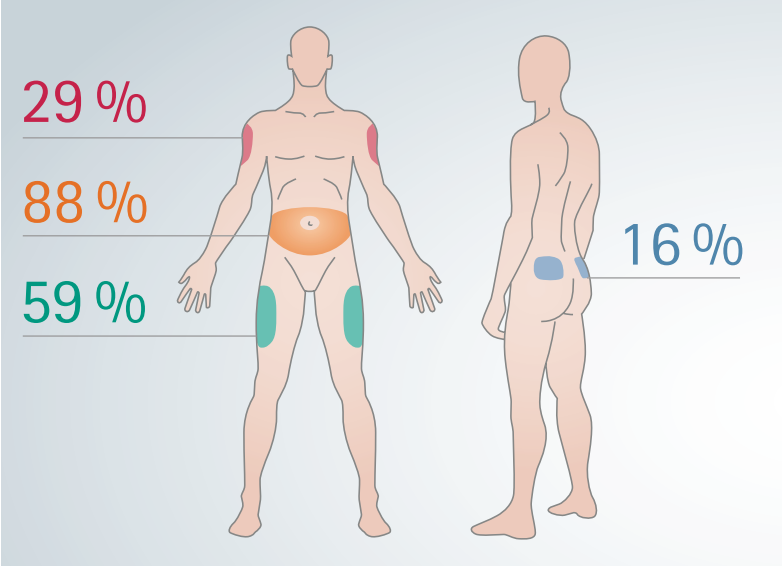
Several types of pen needles are currently available for insulin injection. Traditionally, most patients with diabetes mellitus used long pen needles with 8 to 12.7 mm length. Over the past few years, science has focused on shorter pen needles. Nowadays, shorter-length pen needles (4 mm and 5 mm) are considered standard for injection technique.

This scientific folder covers the utilization of shorter pen needles in terms of injection sites, injection angles, skin preparation and associated topics such as efficacy, safety, patient satisfaction and preferences. Furthermore, it advises healthcare professionals on the best practice for their patients. All the mentioned factors play a major role in the efficiency of insulin doses and make clinical training especially valuable.

All information in this folder is obtained from recently published studies in order to give a comprehensive overview of the performance and safety of short length pen needles.

2.1.

INJECTION SITES



Preferred injection sites (for children, adolescents and adults, multiple answers were possible) [De Coninck et al. 2010]

DEFINITION

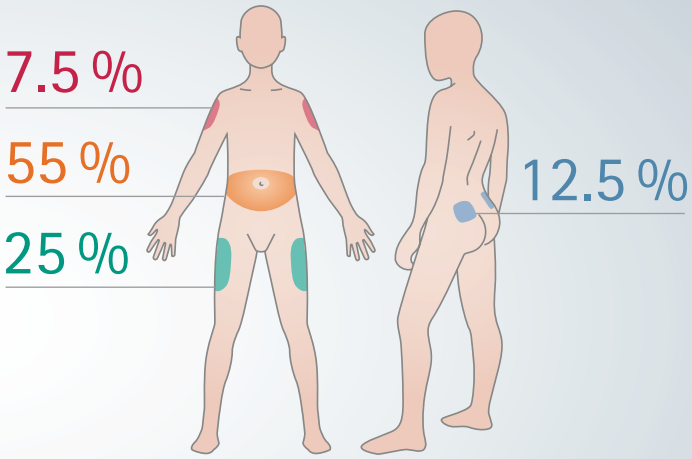
The term injection site is used to describe the preferred body sites for needle placement and injection.

OUTCOMES

Most patients used the following four injections sites [Hirsch et al. 2014]: abdomen, thighs, upper arms, buttocks.

In general, the abdomen and the thighs are the preferred body areas to inject insulin. [Kreugel et al. 2010]
A multinational survey of children, adolescents and adults allowed multiple answers and found the following: the abdomen (with 88 %) was the most frequently used injection site for insulin administration, followed by the thighs with 59 %, the arms with 29 %, and the buttocks with 16 %. [De Coninck et al. 2010]

Surveys on pediatric populations confirmed these results. In a pediatric population of 40 children and adolescents, the preferred injection sites were the abdomen with 55 % and the thighs with 25 %. The buttocks were less frequently used with only 12.5 %. The arm was only preferred by 7.5 % of all children and adolescents because of the potential risk of intramuscular injections in the arm due to the short distance between the skin and the muscle and the technically difficult procedure of forming a lifted skin fold. [Marran et al. 2014]



An accurate injection technique for subcutaneous insulin administration is important for improved glucose control. The correct procedure includes the preferred injection sites, the injection angle, skin folds (pinch up) and skin conditions.

Preferred injection sites (pediatric populations)
[Marran et al. 2014]

A second trial on pediatric patients showed that the abdomen is the overall preferred injection site. Interestingly, differentiating between preschool children (aged between 2 and 6 years old) and older children and adolescents showed that the arm was used as frequently as the abdomen in preschool children.
[Lo Presti et al. 2012]

To reduce discomfort and adverse effects, the rotation of injection sites is recommended. [Kreugel et al. 2010]

Several patients chose their injection site based on pain (12 %). 21 % of patients stated to have injected into the same site for an entire day or even a few days. One third of patients stated not to have a specific injection routine.

A clinically important aspect for injection procedure is the injection zone. In case of abdominal injections, 82 % of patients prefer large injection zones such as a postcard or a playing-card format. This can be clinically supported because the risk of lipohypertrophy seems to be more frequent in patients using smaller injection zones. 91 % of patients rotate within the same site and 93 % rotate from the left to the right side of their body.
[De Coninck et al. 2010]

PROCEDURE NOTES

The site of injection should be inspected by the patient prior to injection. Injections should be administrated in a clean site using clean hands. The site should be disinfected when found to be unclean or there is a risk of infection (e.g. in hospitals and nursing rooms). Disinfection of the site is not necessary outside the institutional setting.
[Frid et al. 2010]

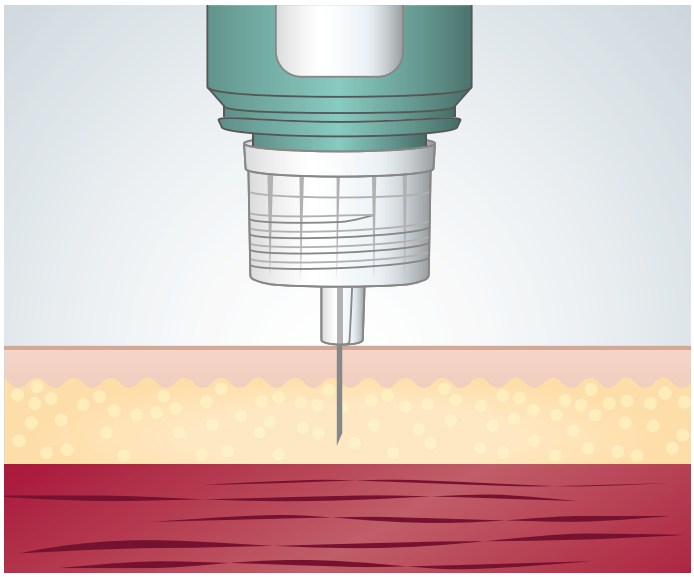
For children or adolescents, arms should only be used for injections if a skin fold can be pinched. This usually requires injection by a third person.
[Frid et al. 2010]

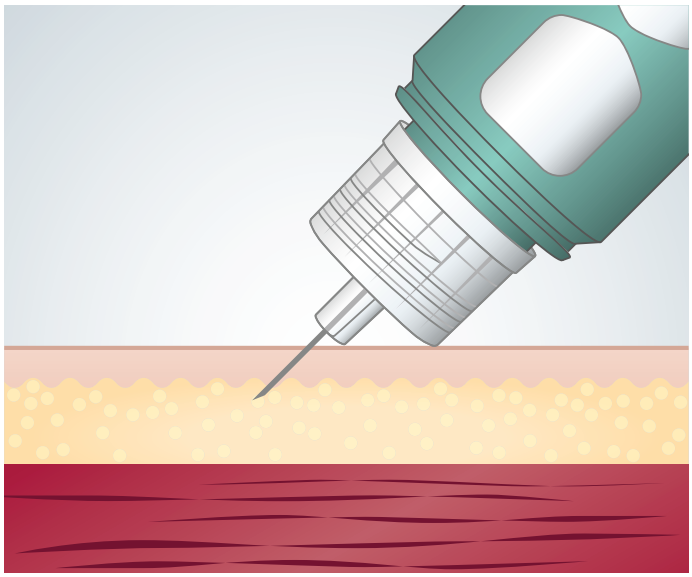
If slim adults prefer injection into the limbs or abdomens, even 4 and 5 mm pen needles may require the use of a skin fold to prevent intramuscular injections.
[Frid et al. 2010]

The best way to preserve normal tissue is to properly and consistently rotate injection sites: dividing injection site into quadrants, using one quadrant per week and moving clockwise. Injections within the quadrant should be spaced at least 1 cm apart to avoid the repetition of a tissue trauma.
[Frid et al. 2010]

2.2.

INJECTION SITE AND ANGLE





DEFINITION

The injection angle is the angle at which the needle is inserted into the human body. Different injection sites require different angles. Also, the length of the needle influences the injection angle.

OUTCOMES

Although the literature disagrees on this topic, several recommendations can be given:

BUTTOCKS

A clear recommendation for different needle lengths cannot be given for the injection site at the buttocks because there is not enough clinical data for a final evaluation. In comparison to the abdomen, arms, and thighs, the buttocks are much less frequently used. [Grassi et al. 2014, Marran et al. 2014]

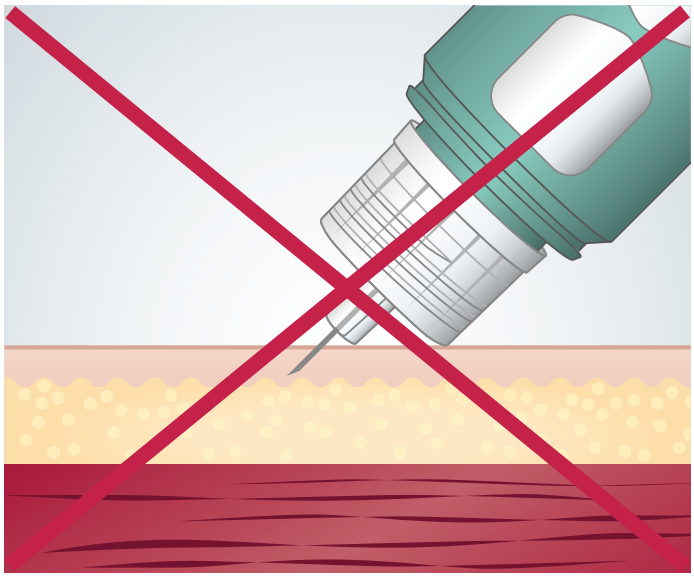
THIGHS

The recommended angle for adult patients using pen needles of 4 or 5 mm is 90 degrees to the skin surface without lifting a skin fold. [Lo Presti et al. 2012, Kreugel et al. 2011, Gibney et al. 2010, Birkebaek et al. 2008] For longer pen needle lengths (6 to 12 mm), the recommended angle is 90 degrees with a lifted skin fold. [De Coninck et al. 2010, Gibney et al. 2010]
For children, thigh insertions should be done at 90 degrees with a skin fold. [Lo Presti et al. 2012, De Coninck et al. 2010]
De Coninck et al. recommend a lifted skin fold regardless of needle length for slim or normal weight children and adults. [De Coninck et al. 2010]
If just 8 mm pen needles are available for children, they should be used with a skin fold and injected at 45 degrees. [Frid et al. 2010]

ABDOMEN

The recommended angle for adult patients using pen needles with a length of 4 or 5 mm is 90 degrees to the skin surface without lifting a skin fold. [Grassi et al. 2014, Hirsch et al. 2014, Lo Presti et al. 2012, Kreugel et al. 2011, Gibney et al. 2010, Frid et al. 2010, Hirsch et al. 2010, Birkebaek et al. 2008]
The same applies to 6 mm pen needles which should be injected at an angle of 90 degrees without a pinched skin fold in adults. [Frid et al. 2010]
8 mm, 10 mm and 12 mm pen needles can be used at 90 degrees to the skin surface with a pinched skin fold.
[Kreugel et al. 2011, Gibney et al. 2010, Hirsch et al. 2010]

For children, 4 mm, 5 mm, 6 mm, 10 mm and 12 mm pen needles can be used at 90 degrees with a skin fold. [Lo Presti et al. 2012, Hirsch et al. 2014, Frid et al. 2010]



It is not recommended to insert 4 mm pen needles at a 45-degree angle [Hirsch et al. 2014]

The choice of the injection angle – 45 or 90 degrees – is influenced by the injection site and the needle length.

For children and adolescents 6 mm pen needles may be used at an angle of 45 degrees instead of a skin fold. [Frid et al. 2010]
If just 8 mm pen needles are available for children, the needles should be used with a skin fold and injected at a 45-degree angle. [Frid et al. 2010]

ARM

For adults the recommended angle for pen needles of 4 to 12 mm lengths is 90 degrees with a pinched skin fold. [De Coninck et al. 2010]
Alternatively, 4 mm pen needles can be applied at 90 degrees without a skin fold according to the anatomical conditions. [Gibney et al. 2010]

In children the recommended angle for all pen needle lengths is 90 degrees with a pinched skin fold. [Lo Presti et al. 2012, De Coninck et al. 2010]
If just 8 mm pen needles are available for children, the needles should be used with a skin fold and injected at 45 degrees. [Frid et al. 2010]
Recommendations for 4 mm pen needles are not consistent: One recommendation states that in many children and adolescents an insertion at 90 degrees without a lifted skin fold is possible. [Frid et al. 2010]

PROCEDURE NOTES

4 mm pen needles cannot be inserted at 45 degree because of the physical characteristics of the needle length and hub. [Hirsch et al. 2014]

Avoid denting the skin while injecting children and adolescents; there is a possibility that the needle may penetrate deeper skin structures such as muscle tissue. [Frid et al. 2010]

Currently valid injection guidelines for adults recommend the use of needles with shorter lengths; there is no medical reason for recommending pen needles > 8 mm. [Frid et al. 2010]

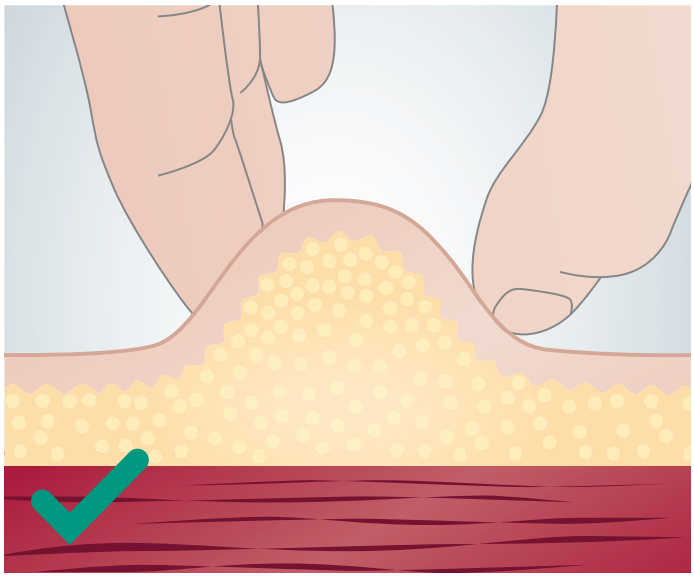
If adults prefer needles ≥ 8 mm, they should lift a skin fold or inject at a 45-degree angle. [Sim et al. 2014, Frid et al. 2010]

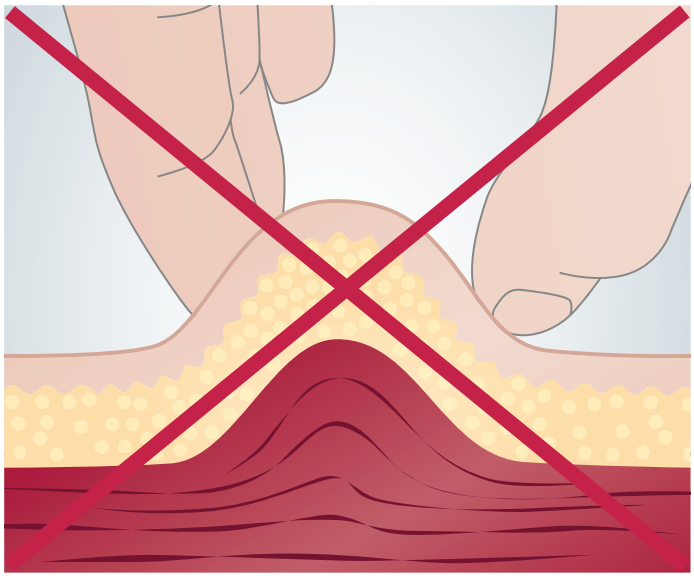
Patients should rotate injection sites within specific body areas. [Kreugel et al. 2011]

Abdomen and thighs are the most recommended injection sites. [Kreugel et al. 2011]

2.3.

SKIN FOLD ("PINCH UP")





DEFINITION

For subcutaneous injection, a skin fold ("pinch up") can be created between the thumb and the index finger (possibly with the addition of the middle finger).

OUTCOMES

Skin folds are used when the presumed distance between skin surface and muscle is less than the length of the needle. Lifting skin folds in the abdomen and thighs is relatively easy. A skin fold is more difficult to do in the buttocks (where it is rarely needed) and virtually impossible to perform properly on the arm. A proper skin fold is made with the thumb and index finger. Lifting skin with the whole hand poses the risk of lifting muscle tissue and of causing an intramuscular injection. [Frid et al. 2010]

A detailed description of injections with or without skin folds for the different injection sites is given in table 1.

In a pediatric population of 40 children and adolescents, who predominantely use 8 mm needles, only 5 % do not use skin folds. [Marran et al. 2014]

A multinational survey of type 1 and type 2 diabetes mellitus patients describes their experience with skin folds. Patients who make a skin fold were asked when they release the skin fold. Most (54 %) said they release it before the injection is finished or right after the injection, instead of holding it for at least five more seconds after the injection has been given. Approximately 20 % of patients use their entire hand to lift a skin fold. [De Coninck et al. 2010]

In a trial on pediatric patients (n = 101) with type 1 diabetes, the children were divided into three groups according to age: 2 to 6, 7 to 13, and 14 to 17 year olds. Most of the children in the youngest group were using 4 mm pen needles, most in the oldest group were using 6 mm needles. In the middle group, 4, 5 and 6 mm needles were used equally. All raised a skin fold. The authors recommend the use of a skin fold for 2 to 6 year old children. Furthermore, the most preferable pen needle for all children appears to be the 4 mm pen needle. [Lo Presti et al. 2012]

<table>
<tr><td rowspan="2">Size</td><td colspan="4">Children/very thin persons</td><td colspan="2">Adults</td></tr>
<tr><td>4 mm, 5 mm</td><td>6 mm</td><td>8 mm</td><td>10 to 12 mm</td><td>4 to 6 mm</td><td>8 to 12 mm</td></tr>
<tr><td>ABDOMEN</td><td rowspan="3">with PU 90°</td><td>with PU 90° or without PU 45°</td><td rowspan="3">with PU 45°</td><td rowspan="3">not recommended</td><td rowspan="3">without PU 90°</td><td rowspan="3">with PU 90°</td></tr>
<tr><td>THIGHS</td><td rowspan="2">with PU 90°</td></tr>
<tr><td>BUTTOCKS</td></tr>
<tr><td>ARM</td><td>with PU 90°</td><td>with PU 90°</td><td>with PU 45°</td><td>not recommended</td><td colspan="2">with PU 90°</td></tr>
<tr><td colspan="7">The upper arm is not recommended, since you would need a second person for the pinch up.</td></tr>
</table>

Table 1 *PU = pinch up

In a multinational survey of 4,352 patients with type 1 and type 2 diabetes mellitus

- 3.6 % of patients use 12.7 mm needles
- 1.8 % use 12 mm needles
- 1.6 % use 10 mm needles
- 48.6 % use 8 mm needles
- 15.8 % use 6 mm needles
- 21.6 % use 5 mm needles
- 7.0 % of patients do not know what length of needle they use.

More than one quarter of thigh injections (27.1 %) were administered without a lifted skin fold and 76 % were administered at an angle of 90 degrees. Only 49 % of subjects who inject into the arm pinch a skin fold. Of those, 66 % inject directly at a 90-degree angle. 55 % of subjects who inject into their buttocks use a pinched-up skin fold; 26 % of all injections into the buttocks are given at an angle of 45 degrees. [De Coninck et al. 2010]

PROCEDURE NOTES

For 4 mm pen needles skin folds are not required.
[Bergenstal et al. 2015, Grassi et al. 2014, Frid et al. 2010, Hirsch et al. 2010]

Very thin or very young children may need a skin fold when using a 4 mm pen needle.
[Bergenstal et al. 2015]

For 5 and 6 mm pen needles skin folds are generally not required for adults and obese patients.
[Frid et al. 2010]

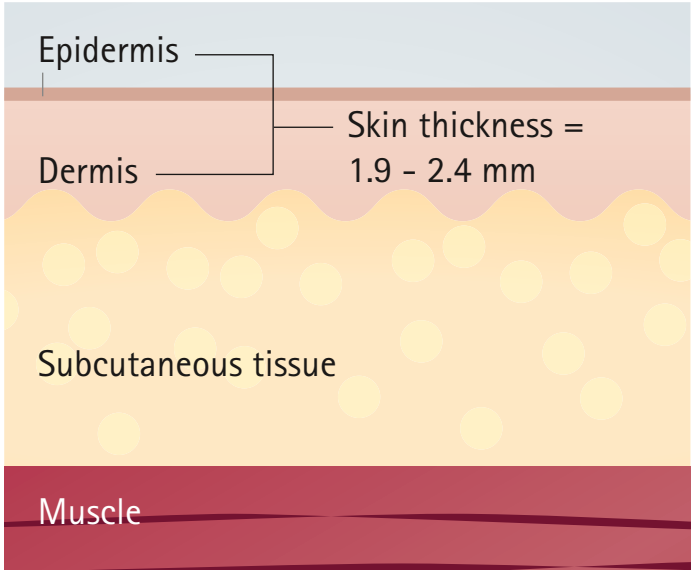
When injecting into the limbs or slim abdomen, 6 mm pen needles should be used either with a skin fold or at a 45-degree angle.
[Frid et al. 2010]

Patients using pen needles ≥ 8 mm should pinch a skin fold or inject at 45 degrees to avoid intramuscular injections.
[Bergenstal et al. 2015, Frid et al. 2010]

2.4.

SKIN AND SUBCUTANEOUS THICKNESS

The thickness of epidermis and dermis at different injection sites is relatively constant across ages, ethnic groups, BMI and gender. It is 1.9 to 2.4 mm on the average and rarely > 3 mm. The thickness of subcutaneous tissue in adults, however, varies depending on gender, body site and BMI.



The thickness of skin is relatively constant
[Grassi et al. 2014, Frid et al. 2010]

DEFINITION

The skin consists of epidermis, dermis and subcutaneous tissue. The skin thickness is made up of the superficial skin (epidermis) and the dermis. The subcutaneous fat layer describes the thickness of the subcutaneous tissue only. Consequently, the distance from the epidermis to the muscle tissue includes the skin thickness and the subcutaneous fat thickness.
[Sim et al. 2014]

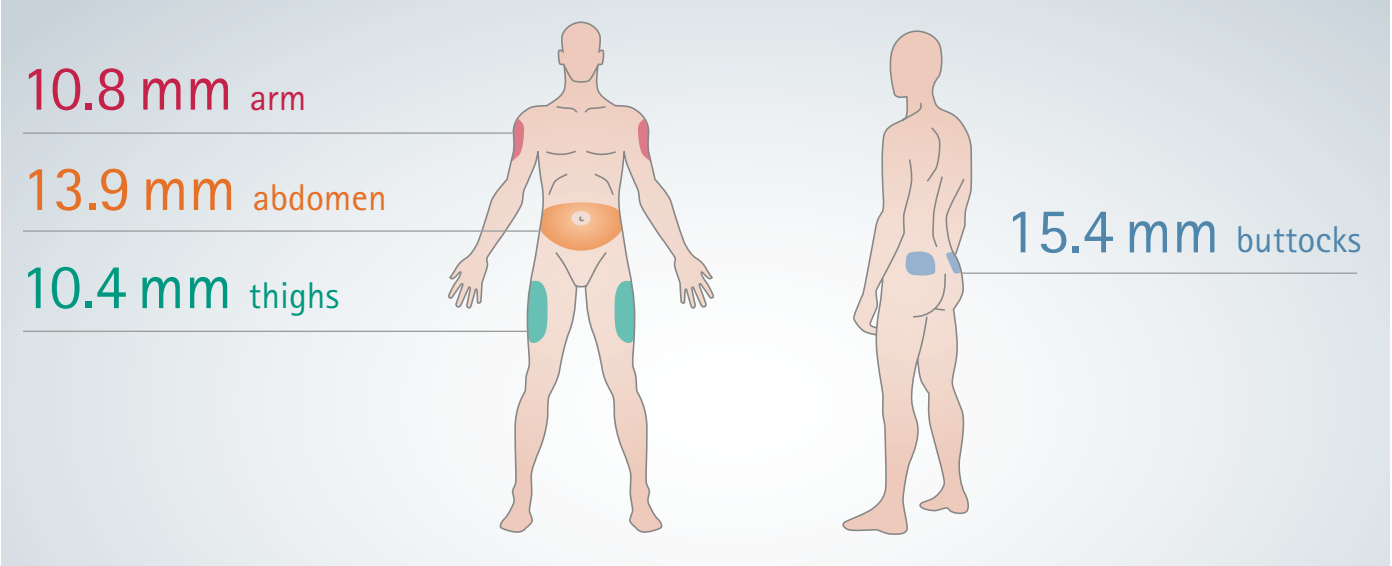
The subcutaneous tissue is the ideal site for the administration of insulin, because blood flow through this fatty layer is slow and predictable. Whereas the flow in the dermis is slow but variable, and blood flow in the muscle is faster and irregular depending on the muscle activity.

OUTCOMES

In general, the skin thickness of different populations in adults with diabetes mellitus has comparable dimensions. [Hirsch et al. 2014, Hofman et al. 2010] Gibney et al. explored the skin thickness of adult diabetes mellitus patients and found mean values of 2.2 mm at the arms, 1.99 mm at the thighs, 2.2 mm at the abdomen, and 2.4 mm on the buttocks. Comparable data could be observed by Sim et al. This working group found a skin thickness of 2 mm on the upper arm and 2.29 mm at the abdomen. However, skin thickness on thighs and buttocks was not evaluated.

The skin thickness among children is slightly lower than in adults and increases with age. The subcutaneous tissue dimensions are comparable in pediatric patients until puberty, as well. After puberty, the subcutaneous fat tissue mass of girls increases while in boys the mass decreases slightly. [Frid et al. 2010]

Marran et al. measured the skin thickness of children and adolescents and found mean values of 1.34 mm at the arm, 1.47 mm at the thighs, 1.65 mm at the abdomen, and 1.79 mm on the buttocks. Furthermore, obese patients' skin dimensions are similar to those of normal-weight and thin patients. [Frid et al. 2010] According to Hofman et al., the thigh skin thickness in adult males is greater than in females (approximately 10 %).



Subcutaneous thickness of adults at different injection sites (mean values) [Gibney et al. 2010]

The thickness of epidermis and dermis at different injection sites is relatively constant across ages, ethnic groups, BMI and gender. It is 1.9 to 2.4 mm on average and rarely > 3 mm at injection sites for insulin. The thickness of subcutaneous tissue in adults, however, varies depending on gender, body site and BMI. [Grassi et al. 2014, Frid et al. 2010]

For example, a clinical study on 341 adult diabetes mellitus patients explored the distance from the epidermis to the muscle tissue.
The median distance from skin surface to muscle tissue is
- 10.9 mm at the thighs
- 12 mm at the arms
- 14.7 mm at the abdomen and
- 16.9 mm on the buttocks.

The absolute minimum distance is at the thigh with 2.8 mm. The absolute minimum distance at the arm, the abdomen and the buttocks was < 5 mm. [Hirsch et al. 2014]

In another study, the subcutaneous thickness of adults at different body sites for injections showed mean values of
- 10.8 mm at the arms
- 10.4 mm at the thighs
- 13.9 mm at the abdomen and
- 15.4 mm on the buttocks. [Gibney et al. 2010]

In a clinical trial, the average subcutaneous thickness at the upper arm is 5.50 ± 2.68 mm and at the abdomen 10.15 ± 6.54 mm. [Sim et al. 2014]

PROCEDURE NOTES

In general, the subcutaneous thickness increased across injection sites in adults and pediatric patients in the following order: arms, thighs, abdomen and buttocks
[Marran et al. 2014]

Several factors affect the subcutaneous fat thickness
- BMI: thickness is higher in patients with a higher BMI [Sim et al. 2014]
- Gender: thickness is higher in females [Sim et al. 2014, Hofman et al. 2010]

A categorizing scheme of the distances from the skin surface to the muscle tissue in < 4 mm and > 6 mm showed:
- The majority of distances were > 6 mm (abdomen 67.9 %, thigh 84.9 %)
- No patients had a skin surface to muscle fascia distance at the thigh < 4 mm
- No adults had a skin surface to muscle fascia distance at the abdomen < 4 mm

[Birkebaek et al. 2008]

3.1.

EFFICACY OF SHORTER P

DEFINITION

Similar to long needles, the efficacy of shorter pen needles depends on a proper injection technique and correct glycemic control.

OUTCOME

Generally, 4 mm pen needles can substantially reduce the risk of inadvertent intramuscular injection if the correct injection technique is used. [Hirsch et al. 2014]
Studies have confirmed equal efficacy as well as safety of and tolerability to shorter pen needles for obese patients.
[Frid et al. 2010]

EN NEEDLES

A questionnaire put to 346 diabetes mellitus patients, who had switched to 4 mm pen needles, showed improved glucose control. Three months after having switched, patients reported mean reductions in HbA_{1c} of 0.58 %, in fasting blood glucose of 14 mg/dL (0.78 mmol/L) and in a total daily insulin dose of 2.0 IU.

Several randomized, controlled studies and surveys have evaluated glycemic control with pen needles of different lengths:

No differences in glycemic control were observed between the 32 Gauge 4 mm and the 31 Gauge 8 mm or 29 Gauge 12.7 mm pen needles in obese patients with diabetes mellitus (randomized, controlled trial on 274 patients). Mean HbA_{1c} levels were slightly lower when 4 mm pen needles were used: -0.08 % and -0.10 % versus the 8 mm and 12.7 mm pen needles, within the equivalence margins. [Bergenstal et al. 2015]

No significant differences in the average fructosamine level and HbA_{1c} level showed between the 33 Gauge 4 mm and the 32 Gauge 4 mm pen needles (randomized, controlled trial on 87 patients). [Valentini et al. 2015]

Similar HbA_{1c} equivalence criteria were evaluated for 31 Gauge 4 mm versus 8 mm and 29 Gauge 4 mm versus 12.7 mm pen needles (randomized, controlled trial on 274 patients). [Strock et al. 2013]

The 32 Gauge 4 mm pen needle provided equivalent glycemic control to the 31 Gauge 5 mm and 8 mm pen needles (randomized crossover trial on 173 patients). [Hirsch et al. 2010]

A subgroup analysis showed equivalent glycemic control for the above named needle sizes in obese and non-obese patients. [Hirsch et al. 2012]

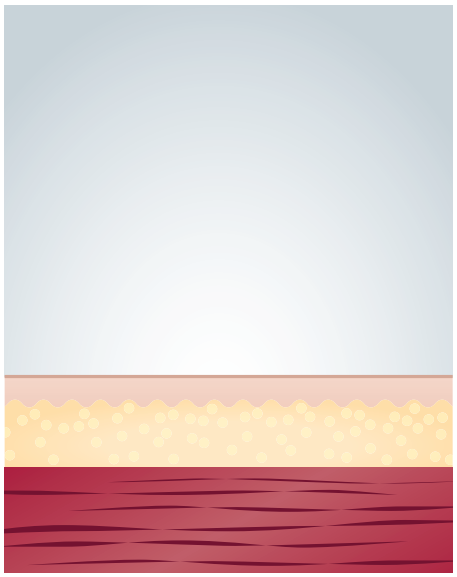
No changes were observed with respect to HbA_{1c}, serum fructosamine, 1.5-anhydroglucitol, and no hypoglycemic events could be observed between 5 mm and 8 mm pen needles (both 31 Gauge; randomized crossover trial on 130 patients). [Kreugel et al. 2011]

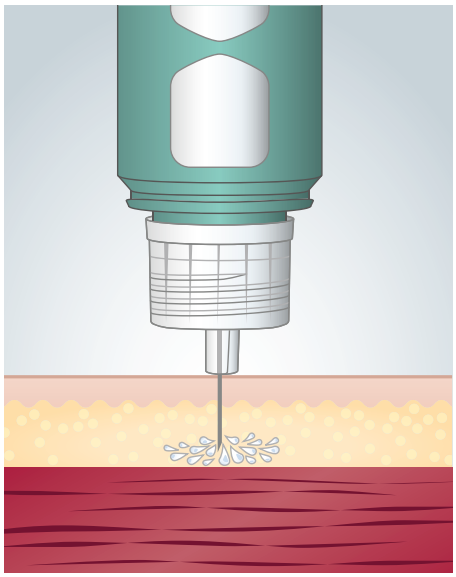
Equivalent glycemic control was found with a 32 Gauge 4 mm and a 32 Gauge 6 mm pen needle (randomized crossover trial on 41 patients). [Miwa et al. 2012]

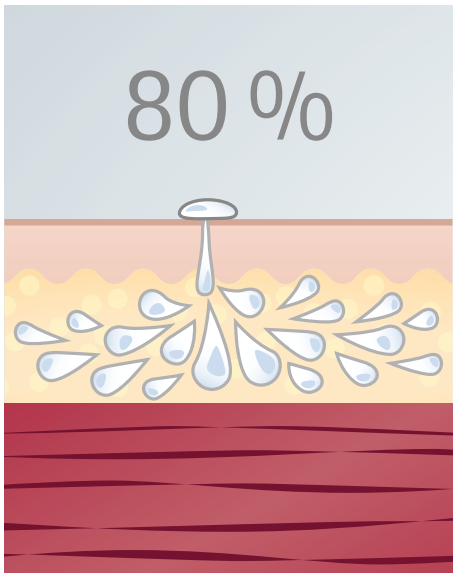
A questionnaire put to 346 diabetes mellitus patients, who had switched to 4 mm pen needles, showed improved glucose control. Three months after having switched, patients reported mean reductions in HbA_{1c} of 0.58 %, in fasting blood glucose of 14 mg/dL (0.78 mmol/L) and in a total daily insulin dose of 2.0 IU. [Grassi et al. 2014]

3.2. SAFETY:

ADVERSE EVENTS AND LEAKAGE







Reported leakage without skin fold
[Hirsch et al. 2010]

DEFINITION

Insulin always should be injected in the subcutaneous tissue without adverse effects. An important adverse event is the leakage of medication – which can affect therapy accuracy.

OUTCOME

The persistent use of 8 mm and 12.7 mm pen needles appears to be based on habit and clinical inertia without any evidence of superior reduction of leakage or backflow from the skin. [Hirsch et al. 2014]

Currently, there is no consistent evidence of an increase in insulin leakage in patient populations using shorter needles of 4, 5, or 6 mm in length. Insulin leakage from the skin with 4 mm pen needles is equivalent to that of injecting with longer, wider-diameter needles. [Frid et al. 2010]

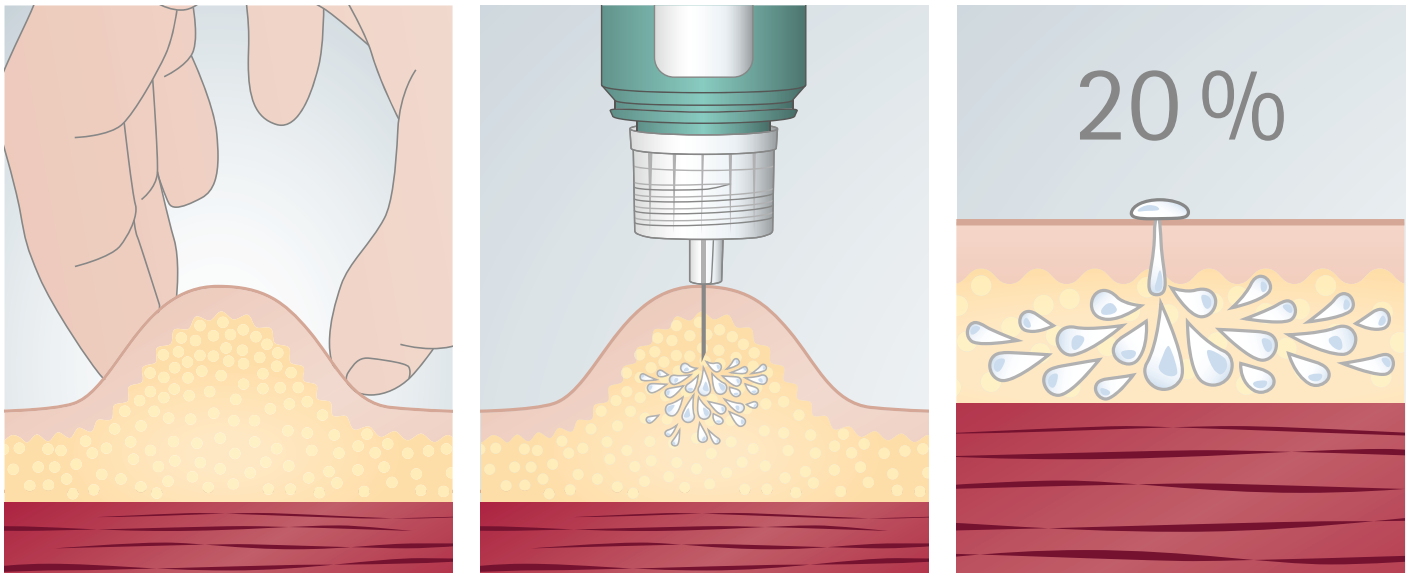
The equivalence of shorter and longer pen needles is based on several clinical trials:

There was no significant difference in reported leakage rates between the 32 Gauge 4 mm and the 31 Gauge 8 mm or 29 Gauge 12.7 mm pen needles, with differences ranging from 4.1 % to 4.3 % of injections. Leakage volumes were significantly larger with the 12.7 mm than with the 8 mm and 4 mm pen needles. Injections reported to have leaked had a significantly greater mean insulin dose than injections without reported leakage from the pen needles. [Bergenstal et al. 2015]

No difference in insulin leakage was observed between the 33 Gauge 4 mm and the 32 Gauge 4 mm pen needles (risk excess: 17 %). The subgroup analysis confirmed this risk excess in patients administering higher insulin doses. [Valentini et al. 2015]

Leakage from the skin was significantly reduced with extra-thin wall 32 Gauge 4 mm, 31 Gauge 5 mm and 31 Gauge 8 mm pen needles in comparison to conventional pen needles with 32 Gauge 4 to 8 mm, 31 Gauge 4.5 to 6 mm and 31 Gauge 8 mm pen needles. [Aronson et al. 2013]

The explored pen needles (32 Gauge 4 mm, 31 Gauge 5 mm and 8 mm pen needles) reported similar injection site leakage. 58 % of the leakage was observed when using 5 and 8 mm pen needles. [Hirsch et al. 2010]



Reported leakage with skin fold
[Hirsch et al. 2010]

A subgroup analysis showed fewer total leakage events when using the 4 mm pen needle in obese and non-obese patients. [Hirsch et al. 2012]

A comparison of 5 mm and 8 mm (each of 31 Gauge) pen needles showed less insulin leakage with the 8 mm pen needle. There was no correlation (for both needle lengths) between insulin leakage from the skin and parameters such as BMI, waist-to-hip ratio, HbA_{1c}, the total amount of daily administered insulin, or the injection site. [Kreugel et al. 2011]

In a crossover study on adult diabetes patients, insulin leakage was rare and no significant differences could be observed between 4 mm and 6 mm (each of 32 Gauge) pen needles. Nevertheless, leakage was numerically higher in the 4 mm pen needle group. [Miwa et al. 2012]

The incidence of leakage differs considerably between different clinical trials.

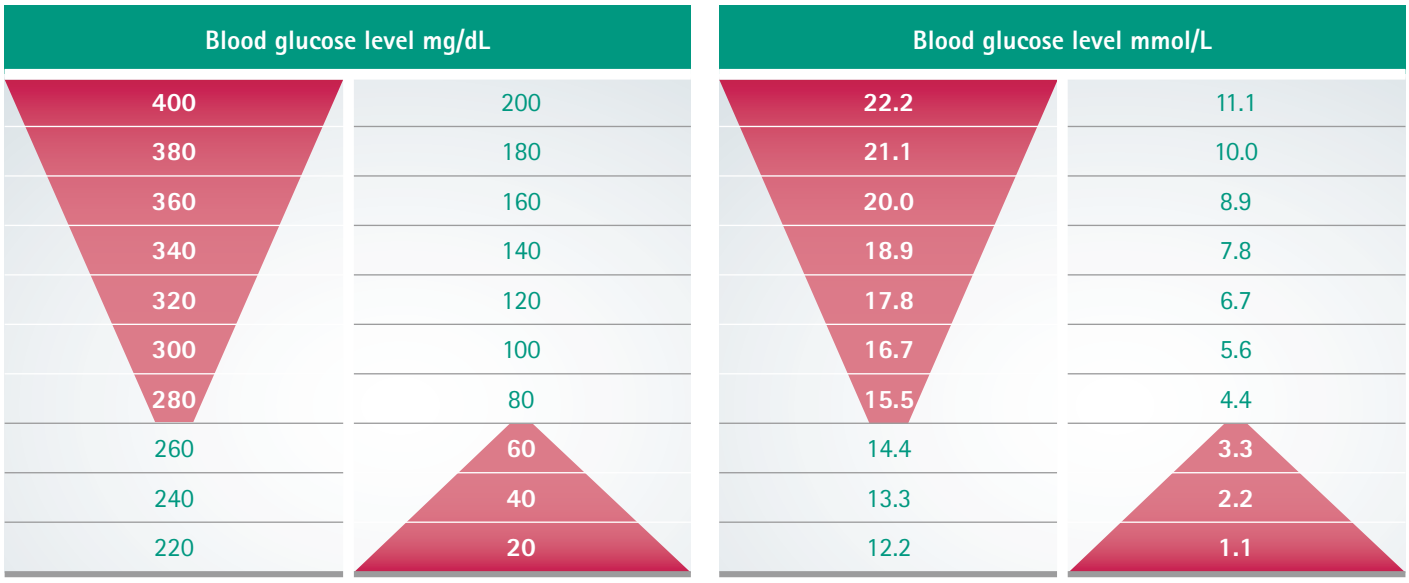
A survey of 4,352 insulin-injecting type 1 and type 2 diabetes patients described a rate of nearly 43 % of patients with insulin leakage from their pen needles after injection. There was no relationship detected between the time that the needle was kept under the skin and the degree of leakage from the site.
[De Coninck et al. 2010]

In a population of 259 patients (122 children/adolescents and 137 adults), adults showed more often insulin leakage than younger subjects (70 % leakage in adults and only 56 % leakage in children or adolescents; significant difference).
The volume of substance given (200, 400, or 600 µl) did not affect the occurrence of leakage. Leakage was more likely to occur with vertical injections (65 % for vertical and 59 % for angled injections; significant difference) and with thigh injections (66 % to thigh and 58 % to abdomen; significant difference).
In general, the amount of leakage recorded in each case was minimal. [Hofman et al. 2010]

A comparison of 32 Gauge 4 mm, 31 Gauge 5 mm and 8 mm pen needles showed that nearly all leakage reports were with injections at 90 degrees. Moreover, about 20 % of events reported with 4 mm and 5 mm pen needles were with lifted skin folds, and 80 % without skin folds. [Hirsch et al. 2010]

3.3. SAFETY:

ADVERSE EVENTS, HYPO-/HYPERGLYCEMIA



DEFINITION

Hyperglycemia is defined as an excessively high blood glucose level and hypoglycemia is described as an excessively low blood glucose level.

The corresponding blood glucose level for hyperglycemia is > 400 mg/dL, and < 50 mg/dL for hypoglycemia. [Bergenstal et al. 2015]

OUTCOMES

In diabetes mellitus patients, hyperglycemia is usually caused by low insulin levels. While there are many reasons, hypoglycemia can be provoked by intramuscular injections. [Hirsch et al. 2014]

Bergenstal et al. explored three pen needle sizes (4 mm, 8 mm, and 12.7 mm) in a randomized crossover study and found that the most frequently reported adverse events were hyperglycemia, hypoglycemia, and upper respiratory tract infections. Hyperglycemic and hypoglycemic adverse events (per 1,000 patient days) did not differ between the pen needles under evaluation. [Bergenstal et al. 2015]

In a further comparison of 32 Gauge 4 mm, 31 Gauge 5 mm and 8 mm pen needles, hypo- and hyperglycemic adverse events were infrequent and did not differ between the different needle sizes. [Hirsch et al. 2010]

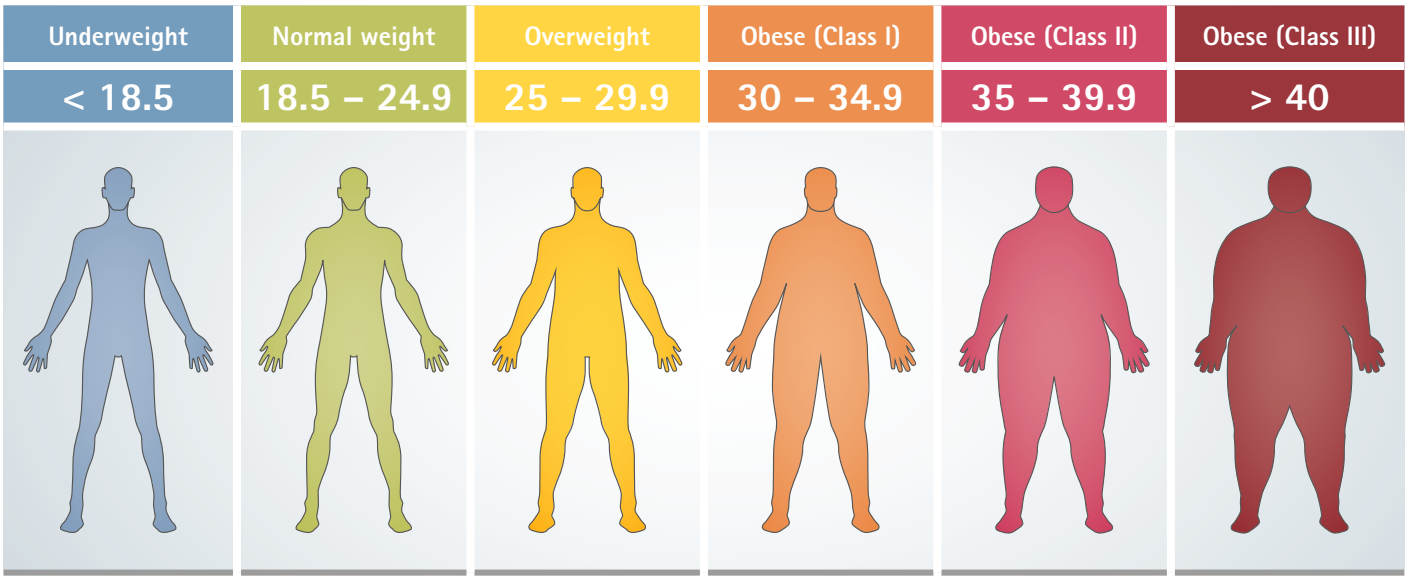
These results were confirmed by Kreugel et al. In their comparison, 5 mm and 8 mm (each of 31 Gauge) pen needles showed no difference in hypoglycemic events. [Kreugel et al. 2011]

No significant difference in hypoglycemia events was observed between the 33 Gauge 4 mm and the 32 Gauge 4 mm pen needles. The study shows that there was a trend towards higher risk when using 32 Gauge needles. [Valentini et al. 2015]

The comparison of extra-thin-wall pen needles (32 Gauge 4 mm, 31 Gauge 5 mm and 31 Gauge 8 mm) with conventional pen needles (32 Gauge 4 to 8 mm, 31 Gauge 4.5 to 6 mm and 31 Gauge 8 mm) showed that the most frequent adverse events were hypoglycemia (8.3 % of patients using the extra-thin pen needles and 6 % with the usual pen needles) and hyperglycemia (2.9 % with extra-thin pen needles and 4.1 % with usual pen needles; no significant difference). [Aronson et al. 2013]

3.4. RISK:

BMI AND OBESITY



DEFINITION

The prevalence of type 2 diabetes mellitus is increasing because of the growing number of overweight and obese individuals. The success of insulin therapy should be the concern of both physicians and healthcare professionals as well as of patients with diabetes mellitus. Connected with this is the question of whether obesity and a higher BMI influence therapy success.

OUTCOMES

Anatomically, obese patients have similar skin dimensions to normal weight and thin patients. [Frid et al. 2010]
It is also known that there is an inverse risk of intramuscular injection with an increasing BMI. Patients with a lower BMI score of < 25 have a higher risk of intramuscular injection than obese patients at any injection site and regardless of needle length. [Hirsch et al. 2014]

Bergenstal et al. evaluated adult diabetes mellitus patients with a BMI of 30 or greater (mean BMI: 37) using three different pen needle sizes (4 mm, 8 mm, and 12.7 mm) and found no interaction between BMI and leakage rates. [Bergenstal et al. 2015]

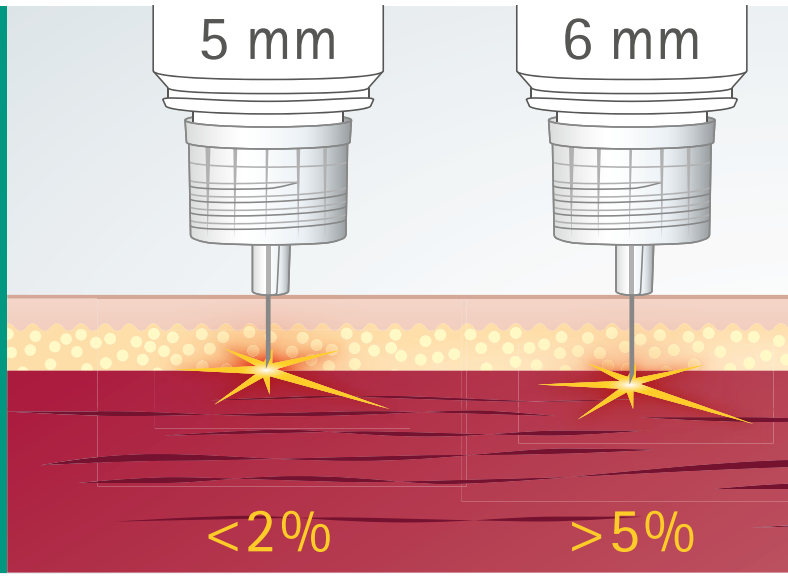
Furthermore, there was no relationship between HbA_{1c} level and BMI on children with type 1 diabetes and the use of 4 mm, 5 mm, and 6 mm pen needles. [Lo Presti et al. 2012]

A head-to-head comparison of obese (35.0 ± 4.9 kg/m^2) and non-obese patients (25.9 ± 2.3 kg/m^2) with different pen needle lengths (4 mm, 5 mm and 8 mm) found more leakage events in patients with BMI > 30 for all lengths. [Hirsch et al. 2012]

3.5. RISK:

INTRAMUSCULAR INJECTIONS

Pen needle length and injection angle have an important influence on inadvertent intramuscular injections.



Risk of intramuscular injection depending on needle length and injection angle [Gibney et al. 2010]

DEFINITION

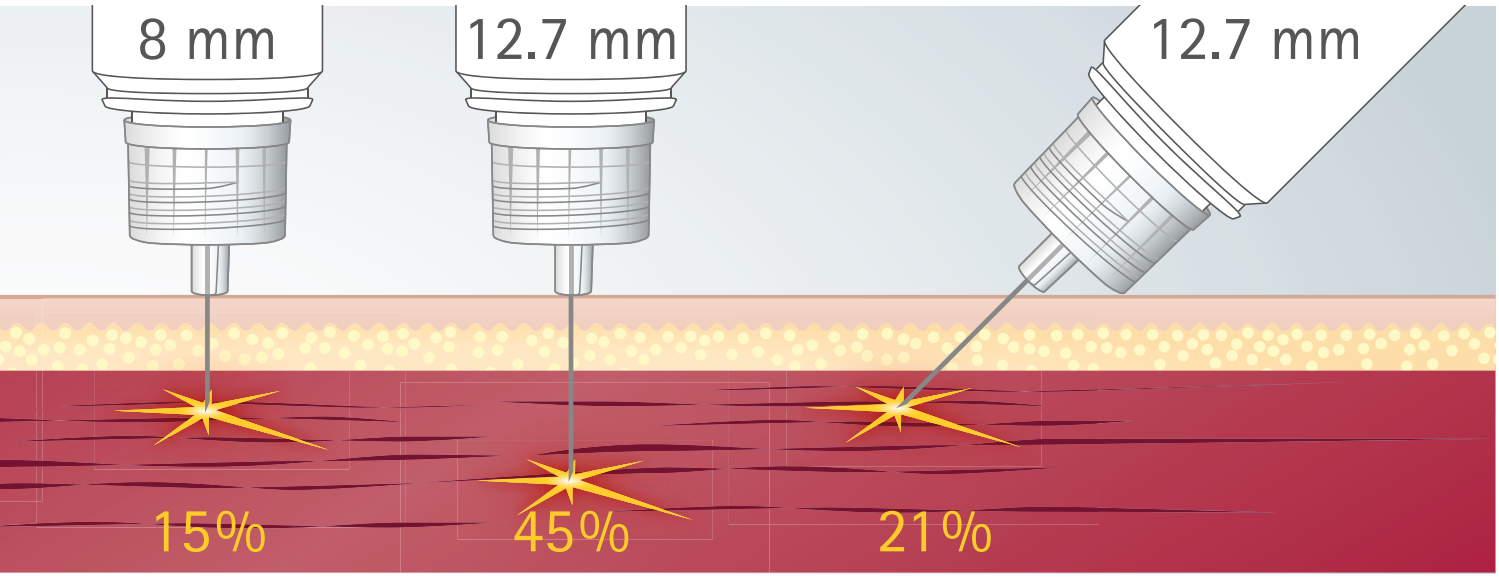
The risk of hypoglycemia is increased by intramuscular injections. These are defined as injections of a substance directly into muscle tissue. In general, intramuscular injections increase insulin absorption and lead to a fall in plasma glucose during muscle exercise.

OUTCOMES

In general, longer needles increase the risk of inadvertent intramuscular injection. [Frid et al. 2010] On the other hand, the risk is substantially reduced with a 45-degree insertion angle. [Hirsch et al. 2014]
A clinical trial on 388 adults with diabetes mellitus (type 1 and type 2) in the US measured needle length and calculated injection tissue depth. The injections were carried out using pen needles of different lengths at 45- and 90-degree angles without lifted skin folds. The results show that more than 98 % of 90-degree insertions with a 5 mm needle are placed in the subcutaneous tissue. Pen needles of 6 mm and 8 mm length have proportionately more injections into muscle (> 5 % and 15 %, respectively). A 12.7 mm pen needle inserted at 90 degrees is intramuscular in 45 % of the cases and even with a 45-degree injection angle, 21 % of injections are still in the muscle. These data support the use of shorter needle lengths. [Gibney et al. 2010]

Additionally, the skin thickness and the thickness of the subcutaneous fat are important factors to consider when choosing a pen needle length and an injection method. The risk of inadvertent intramuscular injection is generally higher if the needle length is longer than skin and subcutaneous fat thickness. [Sim et al. 2014] Therefore, the risk of intramuscular injection is inversely related to the BMI. For a BMI < 25, a 2 to 4 fold greater risk can be observed in comparison to obese patients at any injection site. The estimated risk of intramuscular injections is higher in men than in women, regardless of needle length (men have a 2 to 4 fold higher risk than women). For example, the risk of intramuscular injection at the thigh is estimated to be 40.2 % for men and 13.8 % in women when using an 8 mm pen needle. [Hirsch et al. 2014] The intramuscular injection risk with 4 mm pen needles is < 1 % in women and < 5 % in men across all injection sites. [Hirsch et al. 2014] An important reason is that women have significantly more subcutaneous adipose tissue (approximately 5 mm) than men. [Hirsch et al. 2014]

A comparison of adults and children showed that children had a higher risk of intramuscular injection (5.5 %) than adults (1.3 %). [Hofman et al. 2010] Lo Presti et al. confirmed these results and found that the youngest group of patients has the highest risk. For patients between 2 and 6 years (no pinch up), 20.2 % intramuscular injections occurred when using a 4 mm needles, with a two-fold increase with 5 mm needles and a three-fold increase with 6 mm pen needles. [Lo Presti et al. 2012]



A survey of pediatric patients (40 children and adolescents) estimated the risk of intramuscular injection at the different injection sites. The risk of intramuscular injection is reduced if a 4 mm pen needle is used, but not completely eliminated. Nonetheless, the risk of intramuscular injection was greater with longer needles. [Marran et al. 2014]

Hofman et al. explored the ideal injection techniques using 5 mm needles on 259 patients (122 children or adolescents and 137 adults). There was a significant correlation between age and the likelihood of an intramuscular injection. Intramuscular injection was much less frequent in adults. Despite the relatively small number of intramuscular injections, the results showed a difference in the incidence of intramuscular injections in children and adolescents depending on their gender. In pre-pubertal boys, the site made no difference, but angled and skin-fold injections appeared to reduce intramuscular incidence. Among girls, no intramuscular deposition was recorded when the skin was pinched or the injection was applied to the thigh. [Hofman et al. 2010]

The risk of intramuscular injections varies in correlation with the injection angle and the needle length at each injection site. The risk of intramuscular injection is particularly high at the thighs and lowest on the buttocks. The risk at the arm and abdomen can be classified as "intermediate". [Hirsch et al. 2014]

A clinical trial on 156 type 2 diabetes mellitus patients explored the risk of intramuscular injection based on needle length and body mass index (with 90-degree insertion in the abdomen and upper arm without skin folds).

The risk of intramuscular injection in the abdomen was:
- 1.9 % for 4 mm
- 5.1 % for 5 mm
- 12.8 % for 6 mm and
- 28.8 % for 8 mm pen needles.

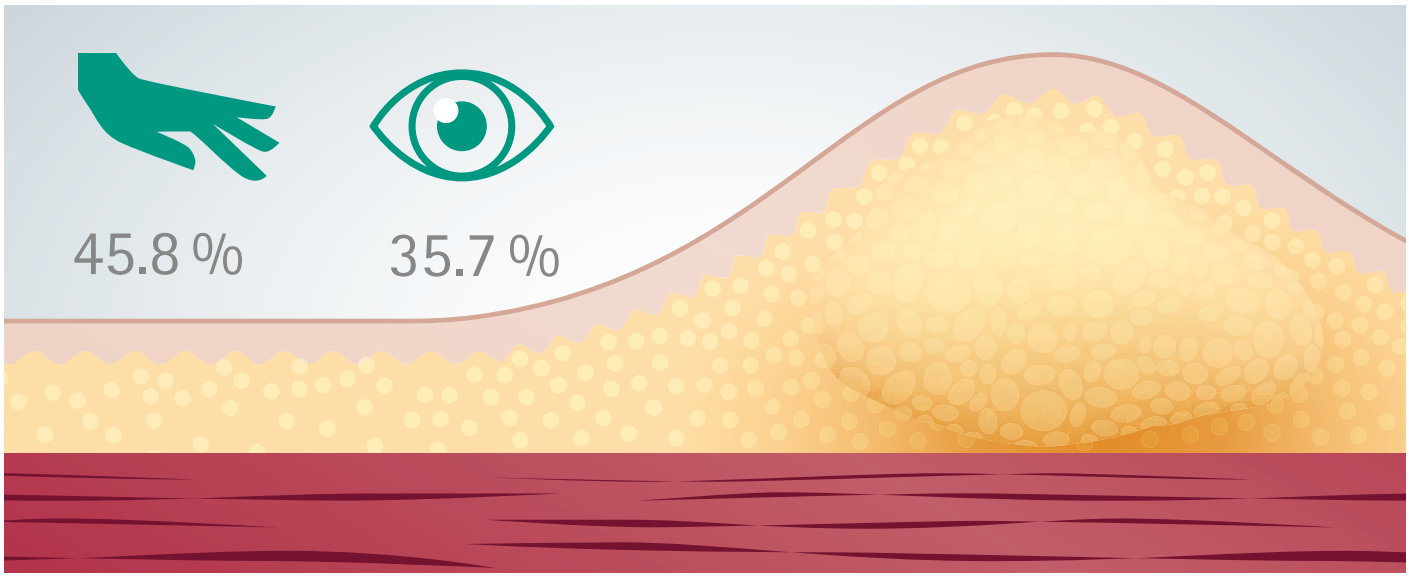
The risk of intramuscular injection in the upper arm was:
- 3.2 % for 4 mm
- 20.5 % for 5 mm
- 35.3 % for 6 mm and
- 58.9 % for 8 mm pen needles.

Furthermore, these results show that the risk of intramuscular injection increases with longer needles in both the abdomen and upper arm. [Sim et al. 2014]

Other authors confirmed the results and concluded that 4 mm and 5 mm pen needles reduce intramuscular insulin injections without increasing the backflow of insulin to the skin surface. [Gibney et al. 2010, Birkenbaek et al. 2008]

3.6. RISK:

LIPOHYPERTROPHY



Ways of identifying lipohypertrophies [Grassi et al. 2014]

DEFINITION

Lipohypertrophy appears as swelling and or hardening subcutaneous tissue at injection sites. A higher frequency of lipohypertrophy is recognized in patients who use a pen needle several times or repeatedly inject in restricted areas. [Ji et al. 2017]

OUTCOMES

In contrast to healthy skin, lipohypertrophic skin cannot be pinched tightly together. In some patients the lesion can be hard or scar like.

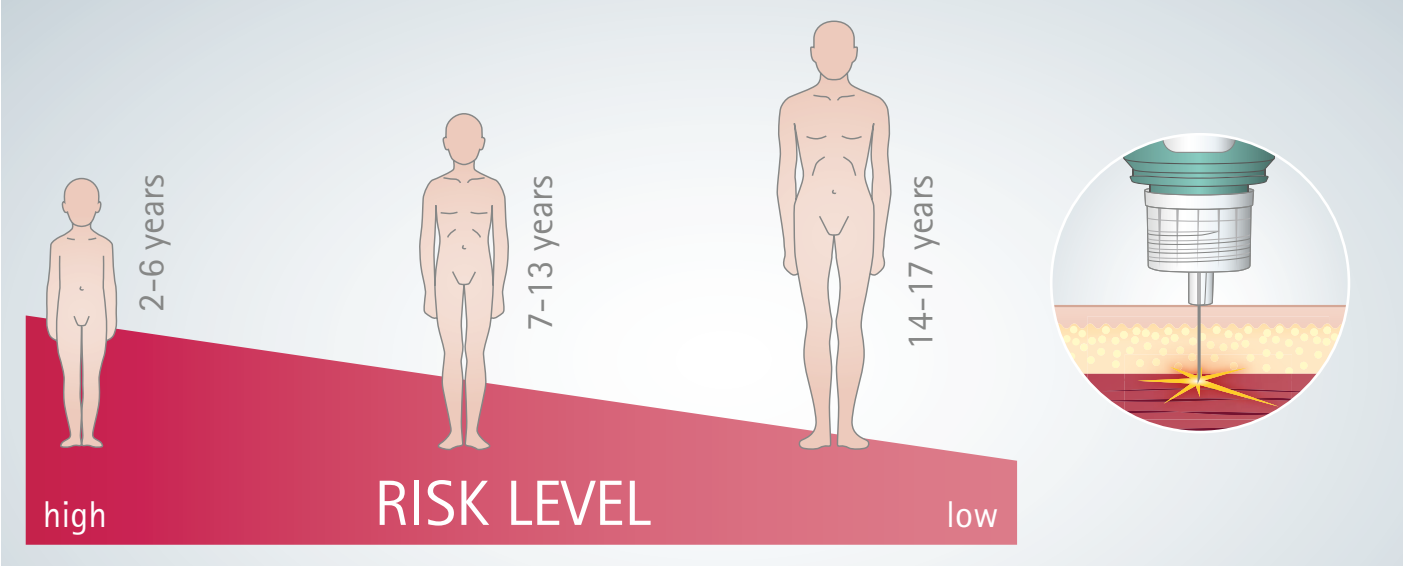
Recently published surveys have highlighted lipohypertrophy as the most common complication resulting from insulin injection. The 2016 "Worldwide Injection Technique Questionnaire Study" of 13,000 patients from 42 countries supports an association between the presence of lipohypertrophy and the use of older, less purified insulin formulations, failure to rotate sites, use of small injecting zones, repeated injection into the same location and reuse of needles. Injections into the lipohypertrophic tissue may also worsen hypertrophy. Therefore, insulin absorption is probably delayed. With respect to this topic, patients should not inject into the lipohypertrophic area until it returns to normal (which takes months to years). [Frid et al. 2016]

Lipohypertrophy is common. A questionnaire put to 346 diabetes mellitus patients found lipohypertrophy in 35.7 % by visual inspection and 45.8 % by palpation. The chance of detecting lipohypertrophy was 48.7 % if visual and touch evaluation were combined. [Grassi et al. 2014]

A comparable overall risk of lipohypertrophy in approx. 50 % of patients was found by a second survey of children, adolescents and adults. Abdominal lipohypertrophy was more frequent when two smaller sized injection zones were used, and the reuse of needles increased the risk as well. [De Corninck et al. 2010]

3.7. RISK:

PEDIATRICS



DEFINITION

Children and their parents are often apprehensive at the beginning of insulin therapy. This apprehension is mostly related to an earlier experience of pain and the negative impact of injections.

OUTCOMES

Fear and anxiety can negatively influence the success of insulin therapy. [Frid et al. 2010]
For children and adolescents, the use of a 4 mm, 5 mm or 6 mm pen needle is recommended, especially for slim patients. Pediatric patients who inject into the limbs may need to lift a skin fold, especially when using a 5 mm or 6 mm pen needle. There is no medical reason for recommending needles longer than 6 mm for children and adolescents. [Frid et al. 2010]

Marran et al. stated that 4 mm pen needles reduced (but did not eliminate) the risk of intramuscular injection. 4 mm pen needles are preferable for children with a lower BMI. [Marran et al. 2014]
Hofman et al. concluded that 8 mm needles have an unacceptable rate of intramuscular injections. Even 6 mm pen needles have a high rate of intramuscular injections when inserted at 90 degrees. In this study, no intramuscular injections were reported with an angled insertion. [Hofman et al. 2010]

A comparison of children aged 2 to 6, 7 to 13, and 14 to 17 years old showed that the youngest group is at greatest risk of intramuscular injections. Interestingly, some children do not insert the needle fully if they feel the procedure to be painful. This impaired technique increases the risk of intradermal injections with a 4 mm pen needle. Children and their parents should be trained in the proper injection technique, including needle insertion to its full length. [Lo Presti et al. 2012]

4. EFFICIENCY OF SHORT

DEFINITION

The success of glycemic control depends on adjustments in the insulin dose, as the daily insulin dose calculation has to reflect individual patient conditions. In their clinical trial, Bergenstal et al. described a range of 6 to 350 IU, with the largest single dose being 100 IU. [Bergenstal et al. 2015]

OUTCOMES

No differences in insulin doses were found between the 32 Gauge 4 mm and the 31 Gauge 8 mm or 29 Gauge 12.7 mm pen needles in obese patients with diabetes mellitus (randomized, controlled trial on 274 patients). [Bergenstal et al. 2015]

Furthermore, the daily insulin dose remained unchanged and did not differ between the 33 Gauge 4 mm and the 32 Gauge 4 mm pen needles (randomized, controlled trial on 87 patients). [Valentini et al. 2015]

A questionnaire put to 259 follow-up patients who switched to a 4 mm pen needle showed no significant differences in total insulin doses after a period of three months. [Grassi et al. 2014]

ER PEN NEEDLES

A questionnaire put to 259 follow-up patients who switched to a 4 mm pen needle showed no significant differences in total insulin doses after a period of three months. [Grassi et al. 2014]

The comparison of 4 mm, 5 mm and 8 mm pen needles did not show a substantial change in insulin doses. Only 21 of 163 patients reported any change in insulin dosage, and only 13 patients reported dose changes > 10 %. [Hirsch et al. 2010]

A randomized crossover trial on 130 patients could not find any changes in insulin doses but the dose was slightly higher with 8 mm pen needles. [Kreugel et al. 2011]

Extra-thin pen needles are able to reduce the time needed to deliver medication by 52 % to 60 % in comparison to regular pen needles. [Aronson et al. 2013]

5.1.

PAIN – DEFINITION AND

For pain intensity measurement, the VAS (Visual Analog Scale) is a unidimensional measurement instrument which is used widely.

Two scales are available: VAS 100 and VAS 150.

DEFINITION

The perception of pain in injection therapy can be influenced by several factors and patient conditions: These include needle length and diameter, and injection technique. Furthermore, pain perception differs between adults and children.
For pain intensity measurement, the VAS (Visual Analog Scale) is an unidimensional instrument which is used widely.
Two ranges are available: VAS 100 and VAS 150.
The VAS 100 ranges between 0 (no pain) and 100 (worst possible pain). The VAS 150 ranges from -75 (much less painful) to 75 (much more painful) and is centered at 0 (as painful as previous needle).

OUTCOME

In general, most injections are not painful, except in the infrequent event that the needle comes into direct contact with nerve endings. Some patients, however, are exceptionally sensitive. [Frid et al. 2010] Children in particular experience more discomfort than adults. The injection angle or site of injection seems to have no bearing on whether the subject feels pain or not. In addition, abdominal injections are less painful than those applied to the thighs. [Hofman et al. 2010]

OUTCOMES

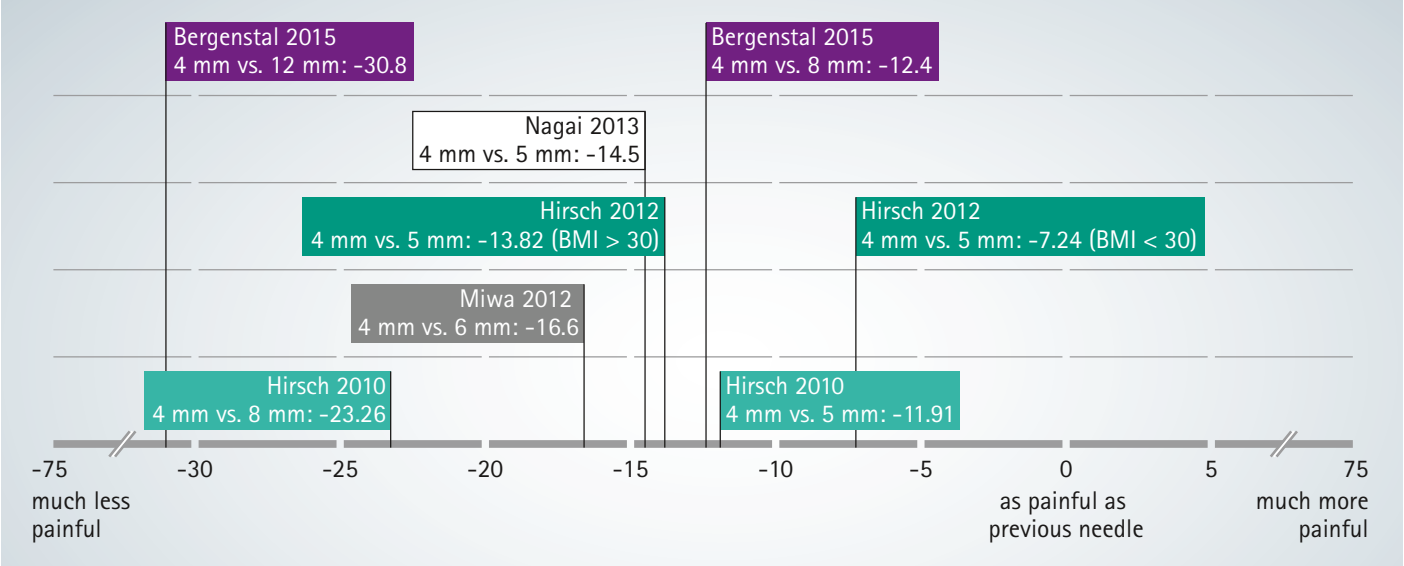


Table 2 | Summarized results on a visual analog scale VAS 150

Randomized, controlled trials and comparative studies evaluated pain perception by using pen needles with different lengths. The results support the assumption that shorter pen needles reduce pain sensations. The detailed findings can be summarized as follows:

Relative injection pain can be assessed using a 150 visual analog scale, which compares injection pain perceived by patients at the end of one period with that in the previous period. Visual analog scale scores range from -75 (much less painful) to 75 (much more painful), with 0 (scale midpoint) meaning "as painful as the previous needle". Bergenstal et al. found that the average pain scores with 4 mm pen needles were significantly lower than with 8 mm, and 12.7 mm needles (4 mm versus 8 mm: -12.4 and 4 mm versus 12.7 mm: -30.8; VAS 150; randomized crossover study; n = 274). [Bergenstal et al. 2015]

Nagai et al. evaluated a 32 Gauge 4 mm (straight wall) needle, a thinner micro-tapered 33 Gauge tip and a 28 Gauge 5 mm needle. The patients perceived less pain with the 32 Gauge 4 mm needle (mean VAS score was -14.5; VAS 150; randomized cross-over study; n = 84). [Nagai et al. 2013]

A 32 Gauge 4 mm pen needle was reported to be less painful than the 31 Gauge 5 mm and 8 mm pen needles (VAS was 11.9 less for the 4 mm versus 5 mm and 23.3 less for 4 mm versus 8 mm; VAS 150; randomized crossover trial on 173 patients). [Hirsch et al. 2010]

A subgroup analysis showed a significant reduction in relative pain for the 4 mm versus 8 mm in obese and non-obese patients. Pain reduction was also observed for patients with a BMI ≥ 30 (in the 4 and 5 mm pen needle group). The VAS pain difference was not significant for subjects with a BMI < 30. [Hirsch et al. 2012]

A clinical trial on 41 diabetes mellitus patients confirmed the above named publications: the 32 Gauge 4 mm pen needle was perceived as being significantly less painful and rated as significantly more favourable than the 32 Gauge 6 mm pen needle (average VAS score for comparative pain was -16.6 mm; VAS 150; randomized crossover trial). [Miwa et al. 2012]

Table 2 shows the above summarized results on a visual analog scale VAS 150. When comparing the results of Bergenstal et al. 2015 and Hirsch 2010 the perceived pain generally seems to be influenced by the applied needle lengths. In the Bergenstal study where 4 mm, 8 mm and 12.7 mm pen needles were applied, the 4 mm versus 8 mm scored much lower compared to the study of Hirsch et al. where the 8 mm pen needle was the longest needle length used next to 4 mm and 5 mm needle lengths. The pain of an 8 mm pen needle seems to be worse when there is no longer needle alternative but only shorter ones.

5.1.

PAIN – DEFINITION AND OUTCOMES

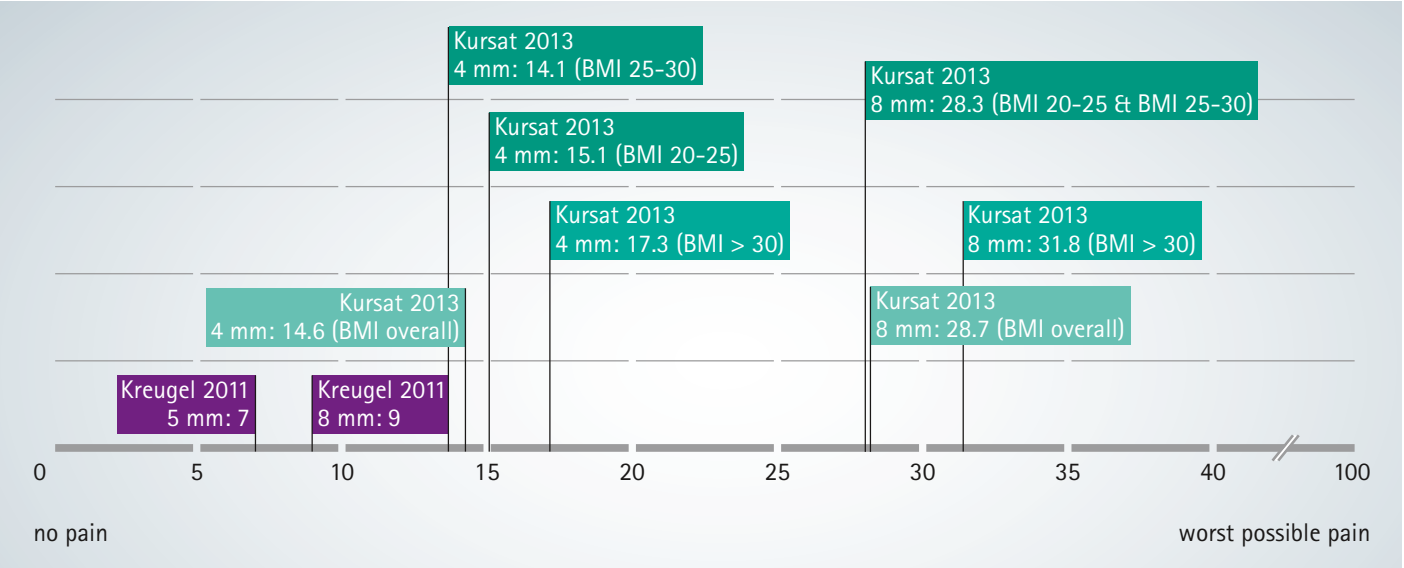


Table 3 | Summarized pain scores on a visual analog scale VAS 100

As an alternative to the 150 visual analog scale for assessing pain, a visual analog scale VAS 100 can also be used, where 0 is "no pain" and 100 is "worst possible pain." In 130 insulin-treated type 1 and type 2 diabetes patients, pain perception was low for both needles (5 mm and 8 mm). A significant difference could not be observed (each of 31 Gauge; randomized crossover trial on 130 patients). [Kreugel et al. 2011]

Also, pain measurement with 4 mm and 8 mm pen needles on 296 diabetes mellitus patients showed higher pain scores with the longer needle (VAS 100). Furthermore, pain perception increases with the age of the patients (for both needle lengths) and with a rising BMI. [Kursat et al. 2013]

Table 3 shows the pain scores on the visual analog scale VAS 100 for the above studies.

PROCEDURE NOTES

A series of recommendations and tips can be given to reduce pain sensations [Frid et al. 2010]:

Keep insulin which is in use at room temperature.

Inject only when alcohol from disinfection has fully dried.

Avoid injecting at hair roots.

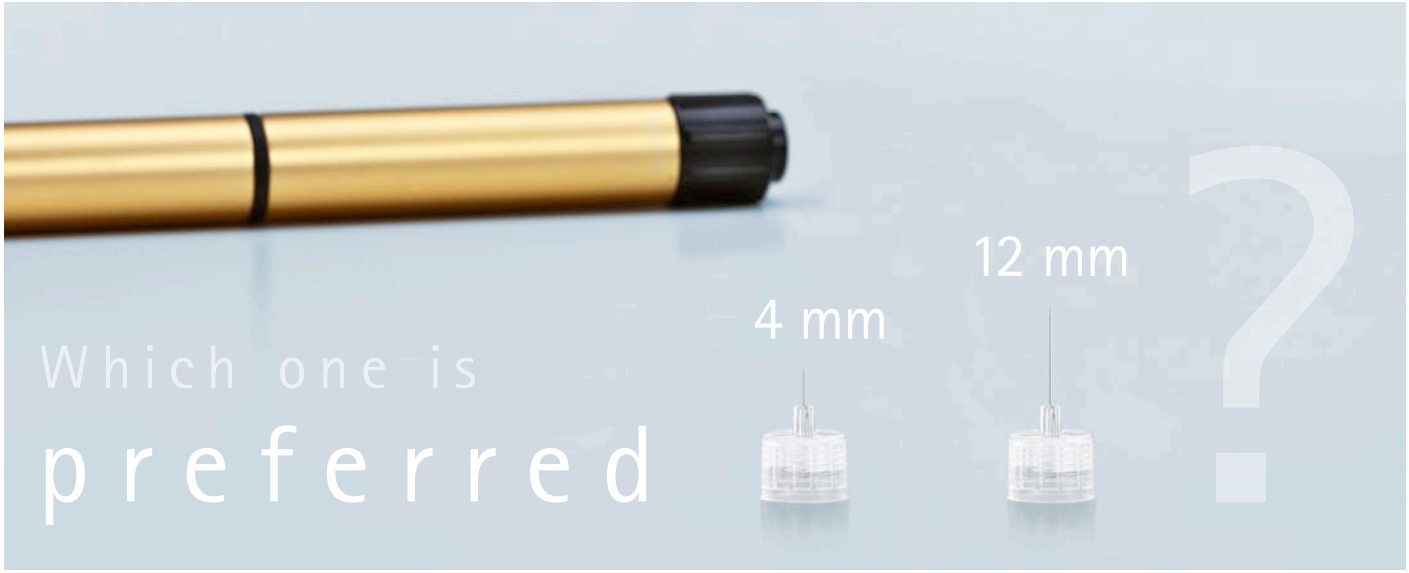
Use shorter and thinner needles.

Use a new needle for each injection.

Insert the needle in a quick dart-like movement, inject slowly; massaging the site before or after injection may speed up absorption.

5.2.

PREFERENCES – DEFINITION AND OUTCOMES



DEFINITION

Understanding patients' preferences for different insulin therapy attributes may improve patients' satisfaction and medication adherence. Today, the overall patient preference for insulin therapy is low due to inconvenience, the possibility of pain during injection and other adverse effects.

OUTCOMES

In recent years, there has been a shift towards shorter pen needles not only as the result of decisions made by healthcare professionals but also due to patients' preferences.

Several publications explored patients' preferences in clinical trials.

In a randomized crossover study on 274 diabetes mellitus patients, significantly more patients preferred the 4 mm pen needle versus the 12.7 mm pen needle. Although more patients preferred the 4 mm needle to the 8 mm needle, this difference was not significant. [Bergenstal et al. 2015]

Approximately 2/3 of patients preferred the 4 mm pen needle in a second randomized crossover study on 173 patients. [Hirsch et al. 2010]

A survey of 259 diabetes mellitus patients showed high levels of satisfaction after switching to a 4 mm pen needle. [Grassi et al. 2014] Furthermore, the overall preference of extra-thin-wall pen needles was 68.2 % versus 11.6 % for conventional needles. The satisfaction parameters "Insertion ease" and "Convenience" also favored the extra-thin-wall pen needles (63.6 % versus 6.1 % and 36.4 % versus 4 % respectively). [Aronson et al. 2013] Also, the comparison of a 4 mm (straight wall) versus a thinner micro-tapered 5 mm needle favored the 4 mm needle in the parameters "Usability" and "Visual impression". [Nagai et al. 2013] A crossover study on adult diabetes patients favored the 4 mm over a 6 mm pen needle in the outcome parameter "Visual impression". Similar ratings were found for needle stability. [Miwa et al. 2012]

A clear patient preference was not observed in all study trials. No specific preference could be found between a 33 Gauge 4 mm and the 32 Gauge 4 mm pen needle. There was a general trend towards the 33 Gauge needle for the parameters "Pain during needle insertion", "Pain during injection", "Ease of needle insertion" and "Global satisfaction". [Valentini et al. 2015] Moreover, there was no significant difference in patients' preferences in a clinical trial of 130 insulin-treated type 1 and type 2 diabetes patients (5 mm versus 8 mm): 46 % of patients preferring the 5 mm needle, 41 % the 8 mm needle, and 13 % did not prefer a particular needle length. [Kreugel et al. 2011]

5.3.

COMPLIANCE – DEFINITION AND OUTCOMES

Compliance outcome parameters are rarely explored in clinical trials.

DEFINITION

Compliance means the voluntary cooperation and adherence of the patient to the therapy regime.

OUTCOMES

Compliance outcome parameters are rarely explored in clinical trials.

Only three clinical trials evaluated compliance-related outcome parameters, such as ease of use, ease of insertion and needle anxiety.

A randomized crossover study compared three pen needle sizes (4 mm, 8 mm, and 12.7 mm) and showed significantly superior ease of use, ease of insertion, and needle anxiety in the 4 mm group in comparison to 8 mm or 12.7 mm pen needles. [Bergenstal et al. 2015]

In a crossover study on adult diabetes patients, a 4 mm pen needle was rated as superior on the outcome parameter ease of use (in comparison to a 6 mm pen needle). [Miwa et al. 2012]

A randomized comparison of a 33 Gauge and 32 Gauge 4 mm pen needle favored the 33 Gauge needle with regard to the parameters: pain during needle insertion, pain during injection, ease of needle insertion, and global satisfaction. [Valentini et al. 2015]

In the future, more clinical data on patient-related outcome parameter such as patients' compliance or patients' satisfaction are needed to understand the patients' preferences and to increase the acceptance of therapy regimes. These qualitative outcome parameters help to increase the cooperation between healthcare professionals and patients.

6.1.

TRAINING

Like the outcome parameter "Compliance", the implementation of training programs is effective in increasing the performance and safety of insulin therapy. However, available data on this topic is rare.

Frid et al. stated in their injection recommendations that education and training are needed for proper and effective use of pen needles. [Frid et al. 2010]
A multicentered questionnaire asked (in a yes or no fashion) if patients had actually been instructed on the injection technique by an educator. It varied hugely between different countries. [De Coninck et al. 2010]
Only one questionnaire answered by 346 diabetes mellitus patients aimed at evaluating the effects of an educational program for injection techniques. Switching to a 4 mm pen needle showed improved glucose control and greater satisfaction with the insulin therapy when training programs were in place. [Grassi et al. 2014]
Another survey (the Swansdown Survey) found that the greatest educational need is detectable in older patients who had been injecting insulin for over ten years and who used outdated practices. [Grassi et al. 2014]
In order to improve the quality of insulin therapy, clinical projects where an educational program must be attended are desirable. Another key aspect is the interaction of educational programs and patient compliance. Especially the question as to whether training can increase patient compliance is worthy of further investigation.

7. CONCLUSION

Diabetes mellitus is an important public health problem affecting the patients' safety. These patients need regular medication by injection. Improvements in injection technique and equipment have increased patient safety and the efficacy of the injections. Shorter pen needles are favored over longer needles which were used in the past.

In a series of recently published clinical trials, 4 mm pen needles have been explored: The efficacy and safety of shorter pen needles have been proven in both adults and children, as well as in obese patients.

Each injection area should be checked individually so an individual decision can be made as to whether a skin fold is recommended and at what angle the needle should be inserted.

Shorter pen needles showed similar glycemic control to longer needles. With the correct technique, 4 mm pen needles are able to reduce the risk of inadvertent intramuscular injection. Furthermore, shorter pen needles are non-inferior to longer pen needles with respect to the risk of adverse effects such as leakage, or hypo- or hyperglycemia. Evaluations of 4 mm, 5 mm and longer pen needles showed no significant difference between the needle sizes with regard to leakage, hypo- or hyperglycemia, and insulin doses.

Needle anxiety and pain are important limiting factors for successful insulin therapy. A series of clinical trials and surveys of patients with diabetes mellitus has demonstrated lower pain perception, greater satisfaction and high acceptance when using shorter pen needles. The implementation of educational programs is also associated with improved glucose control and better injection techniques.

Compliance, efficacy of educational programs, or the interaction between the two, is rarely explored in clinical trials. Further studies are needed to make qualitative evaluations of a patient's outcome parameters with regard to the comfort level of the injection therapy.

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