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# Randomized Trial on the Influence of the Length of Two Insulin Pen Needles on Glycemic Control and Patient Preference in Obese Patients with Diabetes

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## Abstract

***Objective:*** This study determined the influence of needle length for insulin administration on metabolic control and patient preference in obese patients with diabetes mellitus.

***Methods:*** In this multicenter, open-label crossover study, insulin pen needles of two different lengths (5 mm and 8 mm) were compared. A total of 130 insulin-treated type 1 and type 2 diabetes patients with a body mass index $\geq 30\ kg/m^2$ were randomized, and 126 patients completed the study. Patients started using the 5-mm needle for 3 months, after which they switched to injecting insulin with the 8-mm needle for another 3 months, or vice versa. Hemoglobin A1c (A1C), fructosamine, and 1,5-anhydroglucitol were measured, and self-reported side effects and patient preference were recorded.

***Results:*** No within-group changes were observed with respect to A1C, serum fructosamine, 1,5-anhydroglucitol, hypoglycemic events, bruising, and pain. When data of all 126 subjects were pooled, there was a small, but significant, difference between needle lengths (5-mm, A1C $7.47 \pm 0.9\%$; 8-mm, $7.59 \pm 1.0\%$; $P = 0.02$). Patients reported less bleeding with the 5-mm needle ($P = 0.04$) and less insulin leakage from the skin with the 8-mm needle ($P = 0.01$). There were no significant differences in patient preference, with 46% of the patients preferring the 5-mm needle, 41% the 8-mm needle, and 13% not preferring a particular needle length.

***Conclusions:*** A 5-mm needle is similar to an 8-mm needle in obese patients with diabetes with respect to metabolic control, injection-related complaints, or patient preference and can be used safely.

## Introduction

A correct injection technique during subcutaneous insulin administration is important for optimal glucose control.[1–5] Preferred insulin injection sites are the upper arm and the anterior and lateral aspects of the thigh, buttocks, and abdomen.[6] Insulin can be injected with a conventional syringe or with an insulin pen and pen needle. Pen needles vary by length and diameter (gauge). According to a recent study in Europe, 92% of adult patients on insulin treatment were using an insulin pen with a disposable needle, and 63% were using an 8-mm needle or longer.[7] In many countries use of a 8-mm needle or longer is recommended for obese adults.[8,9] The Canadian Diabetes Association writes, "short needles are not suitable for everyone; in people who are overweight, the short needle might not penetrate deeply enough to reach the layer where the insulin can be absorbed into the body."[8] Contrary to the previous assertion, research suggests the needle only needs to pass through the skin, which has been shown to be less than 2.88 mm thick in more than 95% of healthy subjects with a wide range of anthropometric characteristics.[10,11]

Patients injecting insulin can experience local injection-related side effects, such as pain, bruising, and bleeding, but also insulin backflow (i.e., leakage) from the skin after needle withdrawal. Several studies (including one by Schwarz et al.,[12] which compared the use of relatively long needles by obese patients) have reported that the majority of patients prefer to use a shorter needle.[12–16] Nevertheless, there is still some reluctance to recommend the use of shorter needles to obese adults. Therefore, we conducted a randomized study comparing the effects of two insulin pen needles on glycemic control and patient preference in obese subjects with diabetes mellitus.

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This trial is registered at ClinicalTrials.gov with trial number NCT00541372.
Portions of this study have been presented as a poster during the 2009 Scientific Meeting of the American Diabetes Association.

## Research Design and Methods

In this multicenter, open label, crossover study, 130 obese patients with type 1 or type 2 diabetes treated with insulin and using an insulin pen were randomized into two groups. Group A started using a 31-gauge 5-mm insulin pen needle for 3 consecutive months, after which they switched to a 31-gauge 8-mm needle for another 3 months (BD Micro-Fine® Mini and Short insulin pen needles, Becton Dickinson, Franklin Lakes, NJ); group B used these two different needles in reverse order. Patients were recruited from the outpatient clinics of one university medical center and four non-university hospitals in The Netherlands (see Appendix). Male and female patients with type 1 or type 2 diabetes were eligible if they injected insulin with a pen device for at least 1 year, were ≥18 years of age, and had a body mass index (BMI) of ≥30 kg/m$^2$. Exclusion criteria were self-adjustments of insulin doses that were incompletely recorded by the patient, hemoglobin A1c (A1C) levels showing >15% variation during the year prior to inclusion, hypoglycemia unawareness, pregnancy or an intention to become pregnant, hemoglobinopathies, or the presence of lipodystrophy. Patients were advised to use a new needle for each injection and to rotate injections within a specific body area. Thigh and abdomen were the recommended body areas for long-acting and fast-acting insulin, respectively, and these remained unchanged throughout the study. The volume threshold of insulin was 50 IU per injection. With a dose of more than 50 IU patients were advised to split the dose and administer the insulin in two injections within the same specific body area. With the 5-mm needle, patients did not use a skin fold and inserted the needle at an angle of 90°. When using the 8-mm needle, patients were advised to inject in a lifted skin fold.

A1C, fructosamine, and 1,5-anhydroglucitol (1,5-AG) were measured at baseline and after each 3-month treatment period. Both A1C and fructosamine measure the mean blood glucose concentration over a period of time, with A1C measuring control over the previous 2–3 months whereas fructosamine measures control over the previous 2–3 weeks. Another marker of glycemia is plasma 1,5-AG. Levels of 1,5-AG are inversely correlated with glycemia and reflect the 2-h postprandial glucose values of the previous 2 weeks.[17] In addition, information on insulin injection doses was collected, and body weight was measured at each visit. Waist-to-hip ratio (WHR) was measured at baseline. The number of hypoglycemic events and injection-related side effects (bleeding, bruising, and insulin backflow) were evaluated with a validated questionnaire with a 4-point Likert-scale.[14] The degree of pain experienced during insulin injection was measured using a 100-mm Visual Analog Scale (VAS), where 0 is "no pain" and 100 is "worst possible pain." The study was approved by the medical ethics review committee of the University Medical Center Groningen, and all participants gave their written informed consent.

A sample size calculation was made by means of a power analysis with patient's preference as the primary objective. It was thus calculated that 131 patients are needed to demonstrate a preference of 65% (i.e., an absolute difference of 15% compared with 50% in case of no preference) with a power of 85% and a two-sided $P$ value < 0.05. For A1C, 49 patients are needed to show that the treatment with 5-mm needles will not be inferior compared with 8-mm needles, defined as a difference in A1C not exceeding the outer bound of the 95% confidence interval (i.e., 0.4% [SD of the changes within a group of 0.92 and correlation coefficient between two measurements of 0.8; power 85%, bilaterally tested at a 0.05 level of significance]). In this power analysis, intra-individual variation of the glycemic control of patients has been taken into account.

Data are presented as mean ± SD, or median and interquartile range, where appropriate. Paired $t$ test and Wilcoxon's Signed Ranks test were used for within group analysis, and $t$ test, $\chi^2$, and Mann–Whitney U tests were used for between-group analysis, where appropriate. Bivariate relationships between parameters were evaluated by $\chi^2$ test, Spearman's rank correlation analysis, or Pearson's correlation analysis, where appropriate. SPSS (version 16.0, SPSS Inc., Chicago, IL) was used for statistical analysis. The level of significance for all tests was $P < 0.05$.

## Results

Of 130 patients enrolled, 126 with type 1 ($n = 5$) or type 2 ($n = 121$) diabetes with a mean BMI of 36.4 kg/m$^2$ (range, 30.1–62.5 kg/m$^2$) completed the study. Baseline characteristics for the two groups of patients with different sequence of needle use are presented in Table 1. Reasons for not completing the study were no reported reason ($n = 1$), use of an "autocover" needle ($n = 1$), and patient preference ($n = 2$). One patient withdrew because of her impression that glucose regulation was better with the 6-mm needle she used before the start of the study (not supported by any changes in A1C level), and one patient withdrew because she experienced an increase of subcutaneous nodules with the 8-mm needle. There were 34 patients who did not apply the skin fold technique while using a 8-mm needle.

During the study, body weight remained unchanged in both groups, and there were no significant within-group changes of A1C, fructosamine, or 1,5-AG levels (Table 2). The insulin dose in group A was unaffected but was slightly

Table 1. Baseline Characteristics of the Participants According to Treatment Sequence

| *Variable* | *Group A (n = 64)* | *Group B (n = 62)* |
|---|---|---|
| Gender (M/F ratio) | 34/30 | 36/26 |
| Age (years) | 60.3 ± 10.7 | 60.7 ± 11.2 |
| BMI (kg/m$^2$) | 36.7 ± 5.5 | 36.1 ± 5.8 |
| Waist-hip ratio | 1.0 ± 0.1 | 1.0 ± 0.1 |
| Type 1/type 2 diabetes | 3/61 | 2/60 |
| Previously used needles | | |
| Length 5 mm and/or 6 mm | 30 | 36 |
| Length 5 mm/6mm and 8 mm | 3 | 2 |
| Length 8 mm | 30 | 22 |
| Length 12.7 mm | 1 | 2 |
| A1C (%) | 7.7 ± 1.1 | 7.6 ± 0.9 |
| FA (μmol/L) | 265 ± 52 | 266 ± 49 |
| 1,5-AG (mg/L) | 10.4 ± 6.6 | 10.1 ± 5.5 |
| TDI (units/day) | 94 ± 43 | 97 ± 55 |

Data are given as absolute numbers or mean ± SD values. Group A first used the 31-gauge 5-mm pen needle and then the 31-gauge 8-mm pen needle; Group B used them in the reverse order.

A1C, hemoglobin A1c; 1,5-AG, 1,5-anhydroglucitol; BMI, body mass index; F, female; FA, fructosamine; M, male; TDI, total daily insulin dose.

higher with the 8-mm needle in group B only ($102 \pm 63$ vs. $97 \pm 55$ U/day, $P = 0.03$).

When all 126 patients were pooled, mean A1C was slightly lower when using the 5-mm needle: baseline A1C was $7.63 \pm 1.0\%$; after 3 months use of the 5-mm needle was $7.47 \pm 0.9\%$, and with the 8-mm needle it was $7.59 \pm 1.0\%$ ($P = 0.02$ for 5-mm vs. 8-mm). No differences were demonstrated in concentrations of serum fructosamine ($256 \pm 50$ vs. $267 \pm 48$ $\mu$mol/L) and 1,5-AG ($10.6 \pm 6.5$ vs. $10.4 \pm 6.5$ mg/L) when pooled data for 5-mm versus 8-mm needle length were compared.

There were no significant differences in self-reported hypoglycemic events (Table 3) during both periods. Patients reported less bleeding ($P = 0.04$) with the 5-mm needle and less insulin backflow with the 8-mm needle ($P = 0.01$), but no difference in bruising. Pain perception was low for both needles, as reflected by a median VAS score of 7 mm (interquartile range, 0–22) for the 5-mm needle and 9 mm (interquartile range, 0–23) for the 8-mm needle (difference not significant). There was no correlation (for both needle lengths) between insulin backflow from the skin and determinants as BMI, WHR, A1C, the total amount of daily insulin use, injection site, or application of skin fold (the latter injection technique only for the 8-mm needle). As expected, there was a strong correlation between reports of bleeding and of bruising ($r = 0.48$ and 0.53, $P < 0.01$ for the 8-mm and 5-mm needle, respectively). There was no difference in patient preference, with 46% of patients preferring the 5-mm and 41% preferring the 8-mm needle, and 13% of patients expressing no specific preference for either needle length. Needle length before inclusion, WHR, or baseline BMI did not predict patients' preference. Finally, at the individual level there was a strong correlation with respect to the occurrence of hypoglycemic events during the period using the 5-mm or the 8-mm needle ($P < 0.01$). This strong correlation was also seen with respect to the occurrence of bleeding, bruising, backflow of insulin, and pain.

Table 3. Reported Hypoglycemic Symptoms According to Treatment Group

| | *Needle length* | |
|---|---|---|
| | *5-mm (n = 126)* | *8-mm (n = 126)* |
| Never | 56 | 56 |
| Less than once a week | 43 | 53 |
| Once or twice a week | 20 | 12 |
| More than twice a week | 7 | 5 |

$\chi^2 = 3.37$, $P = 0.337$.

## Discussion

In the present study, we compared the effects of using either a 5-mm or an 8-mm needle for injecting insulin in a large group of obese patients with diabetes. Besides a small, but statistically significant, difference of A1C (0.12%, $P = 0.02$) in favor of the 5-mm needle, there were no significant differences in other parameters of glycemic control, incidence of hypoglycemia, or patient preference. In addition, there was no clinically relevant influence of needle length on injection-related side effects.

The absence of effects of needle length on glycemic control is in agreement with the results obtained in other studies.[12,14–16] Schwartz et al.[12] reported a lack of change in A1C in 62 obese patients who used either a 31-gauge 6-mm needle or a 29-gauge 12.7-mm needle, each for 12 weeks. Our group has reported that the use of a 5-mm needle was associated with similar levels of A1C and frequency or severity of hypoglycemic events but less discomfort compared with 8-mm or 12-mm needles in a group of 68 patients with diabetes and a mean BMI of 28.2 kg/m$^2$.[14] In a very recent study, Hirsch et al.[15] reported comparative glycemic control in a 3-week two-period crossover study for a new 32-gauge 4-mm insulin pen needle compared with both 5-mm and 8-mm 31-gauge needles, using serum fructosamine as the measure of glycemic control.

Unique in our study is the 1,5-AG measurement. Because 1,5-AG is influenced by postprandial elevations, any influences of needle length on postprandial glucose levels would be expected to have an influence on 1,5-AG. As reported, there were no changes in 1,5-AG levels.

The percentage of patients preferring the shorter needle is lower than that found in an earlier study by our group in patients with varying degrees of obesity.[14] Schwartz et al.[12] reported a higher preference for a 6-mm needle versus a 12.7-mm needle in obese patients with diabetes mellitus, although

Table 2. Relevant Metabolic Parameters in the Two Treatment Groups After a 3-Month Period of Administering Insulin Injections with 5-mm or 8-mm Needles

| | *Use of needle length* | | | |
|---|---|---|---|---|
| | *Group A (n = 64)* | | *Group B (n = 62)* | |
| *Variable* | *5-mm* | *8-mm* | *8-mm* | *5-mm* |
| Weight (kg) | $110 \pm 16$ | $108 \pm 17$ | $105 \pm 16$ | $104 \pm 16$ |
| A1C (%) | $7.5 \pm 1.0$ | $7.6 \pm 1.1$ | $7.5 \pm 0.8$ | $7.4 \pm 0.8$ |
| FA ($\mu$mol/L) | $259 \pm 59$ | $275 \pm 52$ | $258 \pm 42$ | $252 \pm 38$ |
| 1,5-AG (mg/L) | $10.3 \pm 6.5$ | $10.3 \pm 6.9$ | $10.4 \pm 6.2$ | $11.0 \pm 6.6$ |
| TDI (IU) | $92 \pm 42$ | $88 \pm 40$ | $102 \pm 65$ | $98 \pm 62$* |

Data are mean $\pm$ SD values. Group A first used the 31-gauge 5-mm pen needle and then the 31-gauge 8-mm pen needle; Group B used them in the reverse order.

*$P < 0.05$ versus baseline.

A1C, hemoglobin A1c; 1,5-AG, 1,5-anhydroglucitol; FA, fructosamine; TDI, total daily insulin dose.

it is interesting that the patients did not distinguish between the two different needles when given injections in which they were blinded to the needle used.

In several studies it was reported that using a shorter needle coincided with a lower injection-related pain score.[12–16] In these earlier studies, investigators not only have used needles of different length but also of different diameter, which could influence the results of patient preference and pain scores. In the present study only the length of both needle types was different. This supports the concept that needle diameter is a stronger determinant of injection-related pain than needle length, especially in obese patients. Indeed, several studies reported that a greater outer needle diameter (smaller gauge) was positively and significantly associated with increased pain at the site of insertion.[13,18,19] For example, in the study of Iwanaga and Kamoi[19] patients using a 32-gauge 6-mm needle, which has a smaller diameter, reported a lower pain score than when using a 31-gauge 5-mm needle, with the difference of outer diameter between both needle types being 0.025 mm. However, these authors suggested that the difference in pain score may also be in part explained by a difference in needle manufacturing (standard vs. tapered needle) and coating.[20] In our study only needle length was different; diameter, manufacturing technique, and coating of the needle were similar. Our findings are not dissimilar from those reported by Hirsch et al.,[15] where patients with a BMI of 19.4–64.5 $kg/m^2$ rated the 32-gauge 4-mm pen needle as less painful and preferred it significantly more than the 31-gauge 5-mm and 8-mm comparator needles—all of which had similar manufacturing technique and lubrication. However, both length and diameter/gauge differed in that trial (the 5-mm and 8-mm needles were not compared).

A particular strength of our study is the large number of patients who participated, and the robustness of our findings supporting the safety of the use of short needles even in obese patients. There are also some limitations. Injection-related pain was assessed retrospectively during the second and third visit using a VAS. Such an assessment precludes the possibility of detecting variations in pain intensity between multiple injections and might be prone to recall bias. In addition, occurrence of hypoglycemic episodes was based on patient self-report, and confirmation by self-measurement of blood glucose was not required. This could have resulted in overestimation or underestimation of the hypoglycemia frequency as certain symptoms might have been incorrectly ascribed to a low blood glucose. However, we do not expect that confirmation of all hypoglycemic episodes by measurement of blood glucose would have significantly altered our conclusions because it is unlikely that patient perception in this respect would be different between both study periods.

We conclude that the findings of this study provide strong support for the current Danish guidelines[21] and the new injection recommendations for patients with diabetes[22] emphasizing greater use of shorter-length pen needles. Our data suggest that there is no additional benefit—and no major clinical difference—in insulin action (as reflected by A1C, fructosamine, and 1,5-AG), when insulin is injected with either of the two needle lengths, in an obese population. Contrary to some patient instruction information,[8] the 5-mm needles can be safely used for insulin injections in obese patients with diabetes mellitus.

## Appendix

*Participating centers (diabetes nurse specialists)*

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## Author Disclosure Statement

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