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Original article

Skin and subcutaneous adipose layer thickness in adults with diabetes at sites used for insulin injections: implications for needle length recommendations

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Abstract

Objective:
During subcutaneous insulin therapy, inadvertent intramuscular (IM) injections may increase pain and/or adversely affect glucose control. The most appropriate needle length for patients depends on skin thickness (ST) and the distance to muscle fascia. ST and subcutaneous adipose layer thickness (SCT) were measured in adults with diabetes.

Research design and methods:
A total of 388 US adults with diabetes (in three BMI subgroups: <25, 25–29.9, and ≥30 kg/m^2) with diverse demographic features were evaluated. Each subject had ultrasound measurements of ST and SCT at four injection sites.

Results:
Subjects had BMI 19.4–64.5 kg/m^2, age 18–85 years; 40% Caucasian, 25% Asian, 16% Black, 14% Hispanic; 28% type 1 diabetes. Mean ST (±95% CI) was: arm 2.2 mm (2.2, 2.3), thigh 1.9 mm (1.8, 1.9), abdomen 2.2 mm (2.1, 2.2) and buttocks 2.4 mm (2.4, 2.5). Multivariate analyses showed body site, gender, BMI, and race are statistically significant factors for ST but effects were small. Thigh ST was <0.6 mm thinner than the buttocks. Differences of 10 kg/m^2 account for 0.2 mm ST variation. Mean SCT was: arm 10.8 mm (10.2, 11.3), thigh 10.4 mm (9.8, 10.9), abdomen 13.9 mm (13.2, 17.7) and buttocks 15.4 mm (14.7, 16.2). Females had 5.1 mm greater SCT. Differences of 10 kg/m^2 account for 4 mm SCT variation.

Adverse events:
A few mild hypo- or hyperglycemia events, unrelated to study procedure, were detected and treated before subject discharge from study visits.

Limitations:
Only adults in the US were studied; some measurements could not be obtained on every subject, at every injection site.

Conclusions:
Injection site ST does not differ by clinically significant degrees in demographically diverse adults with diabetes; SCT has a wider range. Needles ≥8 mm, inserted perpendicularly, may frequently enter muscle in limbs of males and those with BMI <25 kg/m^2. With 90° insertion, needles 4–5 mm enter the subcutaneous tissue with minimal risk of IM injection in virtually all adults. These data will assist recommending appropriate length needles for subcutaneous insulin injections in adults.

Introduction

Research starting in the 1980s suggested that injection technique is similar in importance to the type and dose of insulin delivered, for attainment of good glycemic control[1–6]. Ages of patients, gender, body mass index (BMI), dose volume, insulin formulation, and injection technique are identified variables that may impact the pharmacokinetics/pharmacodynamics of insulin[7–14]. Injection technique covers a range of procedures intended to facilitate the most consistent, least painful delivery of insulin into subcutaneous (SC) tissue, including injection site and needle length selection, angle of needle insertion, and use of a lifted skin fold.

Commonly used anatomical sites for SC insulin injections include the upper arm (triceps area), antero-lateral upper thigh, abdomen, and the buttock, typically the upper outer quadrant. Knowledge of the thickness of skin (epidermal-dermal layers) and of the SC adipose layer is essential for optimal development and use of percutaneous drug delivery devices, including hypodermic needles for insulin therapy.

Prior studies investigating ST and SCT usually focused on determining the risk of intramuscular (IM) insulin injections, using either computed tomography or ultrasound[2,12–18]. They have limitations that prevent generalization to the broad adult population with diabetes, such as small sample size, narrow BMI ranges, or restriction to children with type 1 diabetes or to non-diabetic patients, and demographics that did not vary widely. Initially, a high frequency (>30%) of previously-unrecognized IM insulin injections was shown with needles commonly used at the time – 12.7 mm (½ inch) length – which was only partly reduced with 8 mm needles[12–14,16].

Ultrasound has been shown to be an effective and reproducible method to measure ST and SCT[17–24]. Ultrasound frequency output in megahertz (MHz) is inversely proportional to the depth of penetration. ST was measured with high-frequency ultrasound in one recent study but the subjects were not diabetic, few were obese, and the sites measured were selected for their utility in intra-dermal vaccination[17]. Dermal thickness measurements were reported in one study of insulin therapy in obese diabetics but only 42 patients were examined[18]. ST averaged between 1.5 and 2.7 mm at various body sites in these studies[17,18] and SCT was not reported. In two recent studies, children and adolescents with type 1 diabetes had ST of similar dimensions to those noted above[19,20]. The subcutaneous adipose layer depth (down to the muscle fascia) requires a lower frequency ultrasound output for accurate measurement[13,14,17,18].

Understanding the ST and SCT at injection sites in a large, diverse sample of adults with diabetes will provide anatomical evidence on which to base needle length recommendations. It is commonly stated that obese patients 'need' longer needles for delivery of SC medication, including insulin. We therefore specifically sought to study subjects with a range of adiposity, and with otherwise diverse demographic features.

Subjects and methods

Protocol

Adults diagnosed with diabetes for at least 1 year participated in this study, conducted at two investigational sites: Rainier Clinical Research Center, Inc., Renton, WA, and Diablo Clinical Research, Inc., Walnut Creek, CA. We sought more than 350 subjects with at least 100 subjects in each of three BMI subgroups (18–24.9, 25–29.9 and $\geq$30 kg/m^2). There was no upper limit BMI. In addition, the following demographic distributions were sought: 50% female, at least 25% in each of three age groups 18–39, 40–59, and 60–85 years; ~25% in each of the racial/ethnic groups White, Black, Asian, and Hispanic; ~75% diagnosed with type 2 diabetes, and >25% treated with insulin. Potential study subjects were recruited by the two investigational sites using their current diabetic population site databases and IRB-approved local advertisements. Study conduct occurred from April 14 to June 22, 2009, and was in compliance with the Declaration of Helsinki and US FDA Regulations and Guidance, including current Good Clinical Practice Guidelines. The protocol was approved by a central IRB, the Copernicus Group IRB, Research Triangle Park, NC, and all subjects provided written informed consent.

Measurements

Each subject's height and weight were measured on the day of study. Ultrasound was selected to measure ST and SCT due to its documented utility[17–24] and safety. The high frequency Cortex DermaScanC ultrasound unit (Cortex Technology, Hadsund, Denmark) with a 20 MHz transducer (probe) was used for ST (Figure 1A), and the GE LOGIQ e ultrasound unit (General Electric Healthcare, Waukesha, WI, USA) with a 4.5–13.0 MHz probe for SCT measurements (Figure 1B). Prior to use of the ultrasound equipment, the units and operators underwent formal testing to ensure measurement consistency. It was established that the measurement error for ST was within ±0.091 mm and for SCT was within ±2.84 mm.

Specific locations for measurements based on bony landmarks were used where possible to reduce inter-subject measurement variability. Each subject had ST (epidermis-dermis) and SCT measurements at commonly used insulin injection sites – rear upper arm (midsection between the acromion and olecranon processes), anterior upper thigh (mid-distance between the iliac crest and the top edge of

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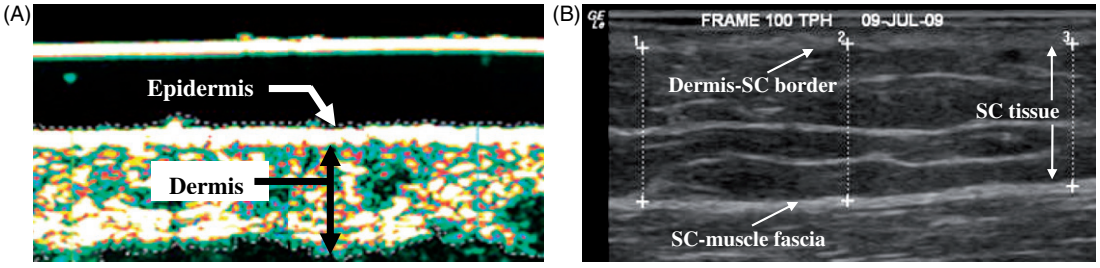

Figure 1. Skin and subcutaneous thickness measurement images. (A): Skin thickness with the Cortex DermaScan C Ver. 3 ultrasound 20 MHz probe. (B): Subcutaneous thickness with GE Logiq e ultrasound 3.7–11.3 MHz probe.

the patella), anterior abdomen (midway between the umbilicus and the iliac crest), and upper outer quadrant of the buttock (middle lower area of the upper outer quadrant). Subjects were randomly assigned to have measurements taken on the right or left side of the body.

After ultrasonic gel was applied, the probe was placed perpendicularly to the predetermined area of the body site. During the scanning process, the probe was moved within the marked area to obtain clear and focused images. The image was obtained using a cine loop setting – a series of approximately 100–200 images frames captured during a single measurement. For ST, the DermaScan unit's software measures the ST across the entire span of the layers within the field of view. The calculated value is the average thickness across the length of the layers within the field of view. For SCT, the GE unit's software measures thickness from a single point along the length of the layers. Three such points were measured from a single image frame to achieve an average SCT value. For the ST and SCT measurements, three frames within the loop were individually measured. The single reading technician selected the three frames using a standardized approach, for measurement consistency. Generally, the first frame was towards the beginning of the cineloop, the second in the middle and the third at the end of the cineloop.

Data analysis

ST and SCT are presented in millimeters. A sample size of 100 in each BMI sub-group allows description of site dimensions with high precision, with 95% confidence margins of ±0.08 mm for ST and ±0.69 mm for SCT. Descriptive statistics for ST and SCT include graphical display, mean, median, standard deviation, minimum, maximum and 95% confidence interval (CI), and are provided for the entire population, for each BMI subgroup, and for other groupings based on gender, age, race/ethnicity, type of diabetes, and use of insulin. In addition, multivariate analyses were done to better weight the statistical and clinical impact of the various inputs, i.e. body site, gender, age, race, BMI, etc, for both ST and SCT. Comparisons of demographic characteristics of various subgroups (based on race, diabetes type, and use of insulin in T2 subjects) were performed using chi-square testing. The threshold for statistical significance is $\alpha = 0.05$, and for clinical significance, minimums of 0.3 mm for ST coefficient and 4.5 mm for SCT coefficient, respectively, were pre-specified.

The factor of race/ethnicity had special handling. Most subjects were White/Caucasian, Asian, Black/African American, and Hispanic/Latino. There were 17 subjects (4%) whose self-classification was outside of these groups, and who were therefore placed into a single 'Other' category – much smaller and more heterogeneous than the four main racial groups. This 'Other' category includes: ten Other/Combination of two or more races/ethnic groups, four Native Hawaiian or Pacific Islander, two American Indian/Alaska Native, and one subject who refused to disclose race. These 17 subjects are included in the overall study population demographics, but are excluded from multivariate analyses due to the very small numbers per race.

A supplementary study was undertaken to provide high-resolution images of SC injections using magnetic resonance imaging. Images were obtained following injection of 40 µL (4 'units') of saline into the middle part of the upper outer thigh in a healthy male. The injections were made with 4 mm, 5 mm, 6 mm, and 8 mm insulin pen needles, and the anatomic deposition of the injected fluid determined.

Adverse events

Subjects' blood glucose was monitored at the completion of ultrasound imaging, by fingerstick blood glucose metering. Readings above 400 or below 70 mg/dL were evaluated and treated according to the site's practices, and blood glucose levels retested prior to subject discharge. The investigator rated each event for severity, for seriousness, and for relation to study procedure.

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Table 1. Demographics – entire study population.

Number of subjects		388
Number with measurements	ST/SCT thickness	341/387
Gender	Male	214 (55%)
Race/ethnicity	White/Caucasian	156 (40%)
	Asian	98 (25%)
	Black/African-American	62 (16%)
	Hispanic/Latino	55 (14%)
	Other/refused to disclose	17 (4%)
Age (years)	Mean (SD)	55.2 (13.4)
	Min/Max	18/85.6
	Median	57.7
Age category (years)	18–39	58 (15%)
	40–59	175 (45%)
	60–85	154 (40%)
Diabetes type	Type 2	280 (72%)
Insulin use in T2 diabetes	Yes	106 (38%)
Height (in)	Mean (SD)	66.1 (4.0)
	Min/Max	54.5/79
	Median	66.0
Weight (lbs)	Mean (SD)	186.5 (48.5)
	Min/Max	100/377
	Median	180.5
BMI (kg/m^2)	Mean (SD)	29.9 (7.1)
	Min/Max	19.6/64.5
	Median	28.6
BMI category	<25	114 (29%)
	25–29.9	110 (28%)
	≥30	164 (42%)

ST, skin thickness; SCT, subcutaneous thickness; SD, standard deviation; Min, minimum; Max, maximum; BMI, body mass index.

Results

Data reconciliation

In the study, ultrasound measurements for ST and/or for SCT were obtained for a total of 388 subjects – there are 387 subjects with SCT data and 341 with ST results. Some images could not be evaluated at the four injection sites for reasons that differed per body site. For SCT, there were 382 readings at the arm; six measurements could not be evaluated. At the thigh, the numbers are 387 and one, respectively; at the abdomen, 375 and 12, respectively; and at the buttocks, 369 and 19, respectively. For ST, there were 322 readings at the arm; 66 measurements could not be evaluated. At the thigh, the numbers are 351 and 37, respectively; at the abdomen, 320 and 59, respectively; and at the buttocks, 264 and 124, respectively. The reader was unable to distinguish between the dermis and SC tissue layers to properly measure buttock ST in an unexpectedly large proportion of cases. A small number of readings were excluded for other reasons.

Subjects' demographics

Table 1 provides demographic characteristics of the entire study population. Mean age was 55 years and ranged from 18 to nearly 86 years; slightly more than half were male. Mean BMI was nearly 30 kg/m^2, and >42% were obese. Higher proportions of subjects in the middle- and older age groups were overweight or obese, than younger-age subjects ($p<0.001$). About 72% were diagnosed with type 2 diabetes and 214 (55%) subjects injected insulin, including 106/280 (38%) subjects with type 2 diabetes. Table 2 provides more detailed data on demographics within racial groups. Caucasians were younger, and Asians older, than Blacks and Hispanics ($p<0.001$). Type 1 diabetes occurred in a much higher proportion of Caucasians than the other three racial groups ($p<0.001$); the proportion of Asians with type 2 diabetes exceeded that in the other groups ($p<0.001$). Greater proportions of African-American and Hispanic subjects had BMI in the obese category (>30 kg/m^2), and smaller proportions had BMI<25 kg/m^2, than Asian and White subjects ($p<0.001$). Table 3 summarizes the demographic data regarding diabetes type and insulin use. Subjects with type 1 diabetes were younger and had lower BMI than those with type 2 diabetes ($p<0.001$). The BMI distribution among type 2 subjects was not significantly different between those who did or did not use insulin.

Skin thickness (ST)

For all subjects and all four injection sites, the mean ST ranged from 1.87 mm (95% CI 1.83, 1.91 mm) in the thigh to 2.41 mm (2.35, 2.47) in the buttocks, shown in Table 4. Raw ST data are displayed in Figure 2A for all subjects, at all four sites, according to BMI. Figure 2B displays raw ST data for all subjects at all four injection sites, according to age. Mean ST results with 95% CIs are shown for all subjects at all four sites according to BMI, gender, race and age groups in Figure 3. Type 2 subjects using insulin have similar ST to type 2 subjects not on insulin, at all four sites (data not shown but available in Supplementary Appendix).

Multivariate analysis demonstrated *statistically* significant impact on ST for the following factors: injection site ($p<0.001$), gender ($p<0.001$), BMI ($p<0.001$), diabetes type and insulin treatment ($p=0.008$), and race/ethnicity ($p=0.009$). Age showed no statistical significance ($p=0.369$). The thinnest ST site is the thigh and the thickest is the buttocks with a difference of 0.57 mm; the arm and abdomen are intermediate. Compared to females, males had slightly thicker skin by 0.3 mm. A change of 10 BMI units (10 kg/m^2) correlates with a change in ST of <0.2 mm. African-Americans had 0.12 mm thicker ST than Caucasians; Asians and Hispanics/Latinos were intermediate. Compared to type 1 diabetes, type 2 subjects – whether or not treated with insulin – have greater ST by 0.1 mm.

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Table 2. Demographics by race.

Characteristic	White	Asian	Black	Hispanic	Other
Number of subjects	156	98	62	55	17
Gender – male	82 (52.6%)	58 (59.2%)	38 (61.3%)	29 (52.7%)	7 (41.2%)
Age (years)					
Mean (SD)	51.8 (15.6)	60.5 (10.9)	54.7 (11.1)	55.2 (11.5)	57.2 (8.6)
Min/Max	18.0/85.6	32.9/84.2	18.6/76.6	24.5/76.2	39.5/74.6
Median	53.5	60.9	55.4	56.3	58.3
Age category					
18–39	43 (27.6%)	4 (4.1%)	6 (9.7%)	5 (9.1%)	1 (5.9%)
40–59	59 (37.8%)	42 (42.9%)	35 (56.5%)	30 (54.5%)	9 (52.9%)
60–85	54 (34.6%)	52 (53.1%)	21 (33.9%)	20 (36.4%)	7 (41.2%)
Diabetes type/insulin use					
Type 1	86 (55.1%)	6 (6.1%)	5 (8.1%)	7 (12.7%)	4 (23.5%)
Type 2: no insulin	41 (26.3%)	66 (67.3%)	32 (51.6%)	28 (50.9%)	7 (41.2%)
Type 2: insulin	29 (18.6%)	26 (26.5%)	25 (40.3%)	20 (36.4%)	6 (35.3%)
Weight (lbs)					
Mean (SD)	184.0 (48.3)	165.8 (36.9)	226.3 (51.8)	190.2 (38.9)	171.2 (38.9)
Min/Max	107/377	107/319	140/376	108/291	100/237
Median	172.0	162.0	224.5	197.0	174.0
BMI (kg/m^2)					
Mean (SD)	28.9 (7.5)	27.7 (4.8)	34.3 (7.9)	31.8 (6.1)	28.8 (6.1)
Min/Max	19.4/62.3	19.4/49.2	20.7/64.5	20.4/49.2	21.6/40.5
Median	26.5	27.1	33.5	32.0	26.8
BMI category					
<25	62 (39.7%)	31 (31.6%)	7 (11.3%)	8 (14.5%)	6 (35.3%)
25–29.9	40 (25.6%)	41 (41.8%)	12 (19.4%)	12 (21.8%)	5 (29.4%)
≥30	54 (34.6%)	26 (26.5%)	43 (69.4%)	35 (63.6%)	6 (35.3%)

SD, standard deviation; Min, minimum; Max, maximum; BMI, body mass index.

Table 3. Demographics by diabetes type/insulin use.

Characteristic	Type 1	Type 2: no insulin	Type 2: insulin
Number of subjects	108	174	106
Gender – male	53 (49.1%)	97 (55.7%)	64 (60.4%)
Race			
White/Caucasian	86 (79.6%)	41 (23.6%)	29 (27.4%)
Asian	6 (5.6%)	66 (37.9%)	26 (24.5%)
Black/African-American	5 (4.6%)	32 (18.4%)	25 (23.6%)
Hispanic/Latino	7 (6.5%)	28 (16.1%)	20 (18.9%)
Other	4 (3.7%)	7 (4.0%)	6 (5.7%)
Age (years)			
Mean (SD)	43.3 (13.6)	59.7 (9.9)	59.9 (10.6)
Min/Max	18.0/72.2	32.6/79.0	32.9/85.6
Age groups			
18–39	49 (45.4%)	6 (3.4%)	4 (3.8%)
40–59	48 (44.4%)	82 (47.1%)	45 (42.5%)
60–85	11 (10.2%)	86 (49.4%)	57 (53.8%)
BMI (kg/m^2)			
Mean (SD)	25.3 (3.9)	31.1 (7.5)	32.5 (6.8)
Min/Max	19.4/40.0	19.4/64.5	20.4/60.8
BMI category			
<25	62 (57.4%)	34 (19.5%)	18 (17.0%)
25–29.9	37 (34.3%)	51 (29.3%)	22 (20.8%)
≥30	9 (8.3%)	89 (51.1%)	66 (62.3%)

SD, standard deviation; Min, minimum; Max, maximum; BMI, body mass index.

Table 4. Skin thickness (mm) by body site.

Site	*n*	Mean	SD	95% CI
Arm	316	2.23	0.44	2.18, 2.28
Thigh	338	1.87	0.39	1.83, 1.91
Abdomen	320	2.15	0.42	2.11, 2.20
Buttock	263	2.41	0.48	2.35, 2.47

n, number of subjects; SD, standard deviation; CI, confidence interval.

Subcutaneous thickness (SCT)

For all subjects and all four injection sites, the mean SCT ranged from 10.35 mm in the thigh to 15.45 mm in the buttocks, a difference of 5 mm. Table 5 includes a summary of mean SCT at the four injection sites for the full study population.

Raw SCT data are shown in Figure 4A for all subjects at all four sites, according to gender. Figure 4B is a similar display of raw SCT data by race (excluding the 17 'Other' group). Mean SCT results with 95% CIs are shown at all four sites for all subjects in Figure 3. The range of SCT measured is much greater than for ST – the 95% CI for mean SCT ranged from 9.79 to 16.19 mm, for all subjects, across all four sites.

In the multivariate analysis, gender had a significant impact on SCT – females have 5.1 mm more SCT than males ($p<0.001$). Injection sites also were significantly correlated with SCT ($p<0.001$). The arm and thigh had similar SCT with the thigh slightly thinner by 0.4 mm. The abdomen was >3 mm thicker than the arm. The SCT of the buttocks, the thickest injection site, was almost 5 mm greater than the arm. BMI, as expected, had a significant impact on SCT ($p<0.001$). An increase of 10 BMI units correlated with a 4 mm increase in SCT.

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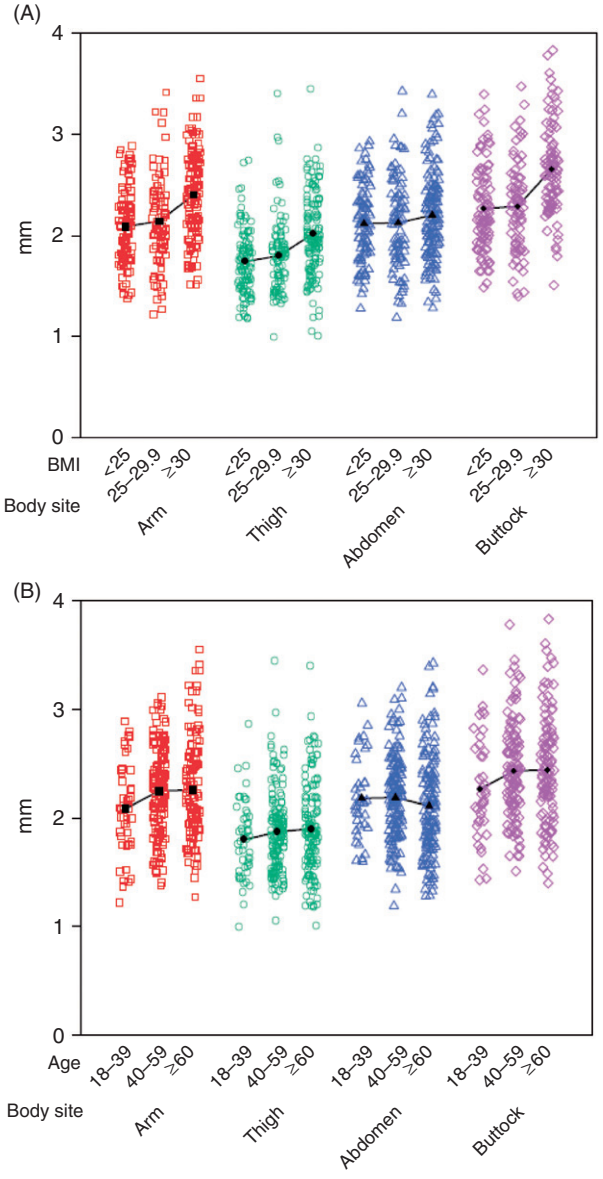

Figure 2. All data points of skin thickness for all subjects at all four injection sites. (A): Data shown according to three BMI subgroups: <25, 25–29.9, and ≥30 kg/m^2. (B): Data shown according to age: 18–39, 40–59, and 60–85 years. Black line connects the means within each injection site.

Age was not significantly related to SCT ($p = 0.45$). Race/ethnicity was statistically significant ($p = 0.038$), accounting for a SCT difference of < 1.2 mm. Type of diabetes and insulin use were significant ($p = 0.013$), and differences were related to injection site. At the abdomen, type 2 subjects had ~5 mm greater SCT than type 1 subjects; at the buttocks, type 2 subjects had ~2.3 mm less SCT than type 1 subjects (See Supplementary Appendix).

Additional findings for ST and SCT by demographic subgroups are provided as a Supplementary Appendix with the online version of this article.

Adverse events

Five subjects had blood glucose levels <70 mg/dL and three had levels >400 mg/dL at study visit conclusion. Subjects received rapidly absorbed carbohydrate or small doses of insulin, respectively, and were discharged only when blood glucose levels were >80 mg/dL or <400 mg/dL. All eight events were rated by the investigators as mild, transient, not serious, and not related to study procedures.

Discussion

Knowledge of injection site skin and subcutaneous thickness in patients with diabetes is essential in the selection of the appropriate needle length and injection technique for insulin injection therapy. The study findings indicate that skin thickness (ST) is very consistent across subjects with diverse demographic features. Conversely, subcutaneous adipose tissue (SCT) varies substantially by certain characteristics (body site, BMI and gender), and much less by age and race. These findings are consistent with those reported in non-diabetic subjects by Laurent *et al.*[17]. In adults with diabetes, ST varies more across body sites of patients with the same demographics than it does between groups of diabetics with very different characteristics (age, BMI, race, etc.).

The original needles for SC injections were much larger diameter (25G) and longer length – up to 16 mm – than today. The need for shorter insulin needles was established in earlier investigations showing a high risk (more than 80% in non-obese children) of intramuscular (IM) insulin delivery with the 12.7 mm (½ inch) insulin needle[13–15]. Shorter-length 8 mm needles were shown to partly reduce this potentially painful event, but still carried an undesirable risk of IM injection, especially for children, adolescents, and thin adults[16,19]. Manufacturers responded with the introduction of even shorter 6 and 5 mm pen needles. Although these needles further reduce the IM injection risk, specific injection techniques including site selection and angling of the injection and/or raising a skin fold are still required for many patients[16,19,20]. Some clinicians have also raised concerns about possible leakage, bruising, and/or intra-dermal medication delivery with 5 mm needles. This ultrasound study of injection sites in adults with diabetes was designed to precisely measure the ST and SCT and provide firm data to support evidence-based insulin injection technique recommendations; to the authors' knowledge, it is the largest such study performed.

ST in a diverse group of adults with diabetes was found to average 2.2 mm in the arm, 1.9 mm in the thigh, 2.2 mm in the abdomen and 2.4 mm in the buttocks. The thinnest mean lower bound 95% CI was 1.8 mm (thigh), and the thickest mean upper bound 95% CI was 2.5 mm (buttocks).

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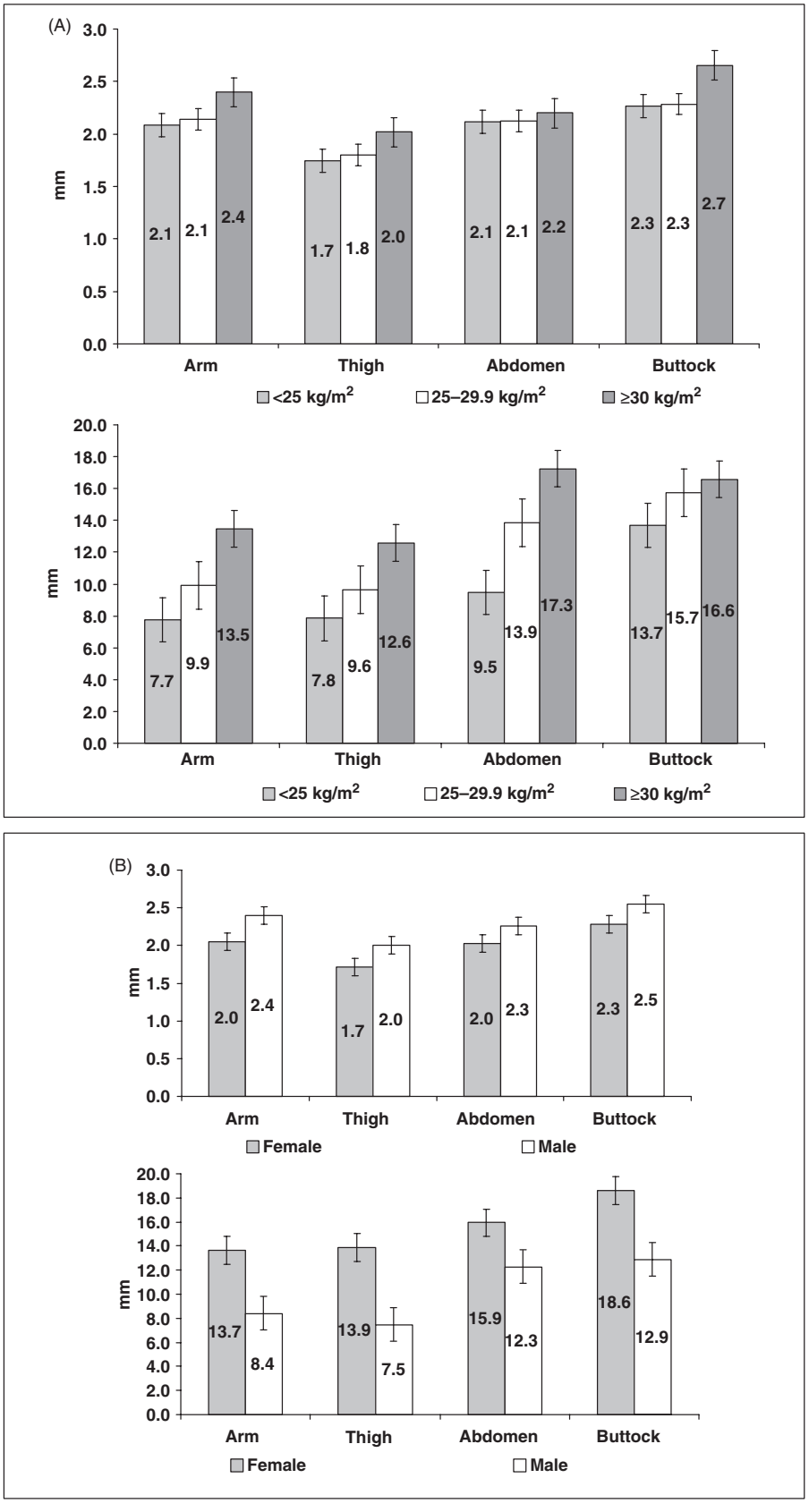

Figure 3. Skin thickness (top) and subcutaneous thickness (bottom) (mean and 95% CI) for all subjects, by injection site. (A): According to BMI. (B): According to gender. (C): According to race. (D): According to age.

Thickest skin appears to be in the buttocks, although measurement precision there is somewhat less compared to the three other sites. These data also indicate a remarkable consistency of ST across important diabetic subgroups. Obese subjects have ST that is barely greater than normal-weight or even thin subjects – multivariate analysis indicates that BMI accounts for very small differences in ST (a change in BMI from 25 to 35 kg/m^2 explains only

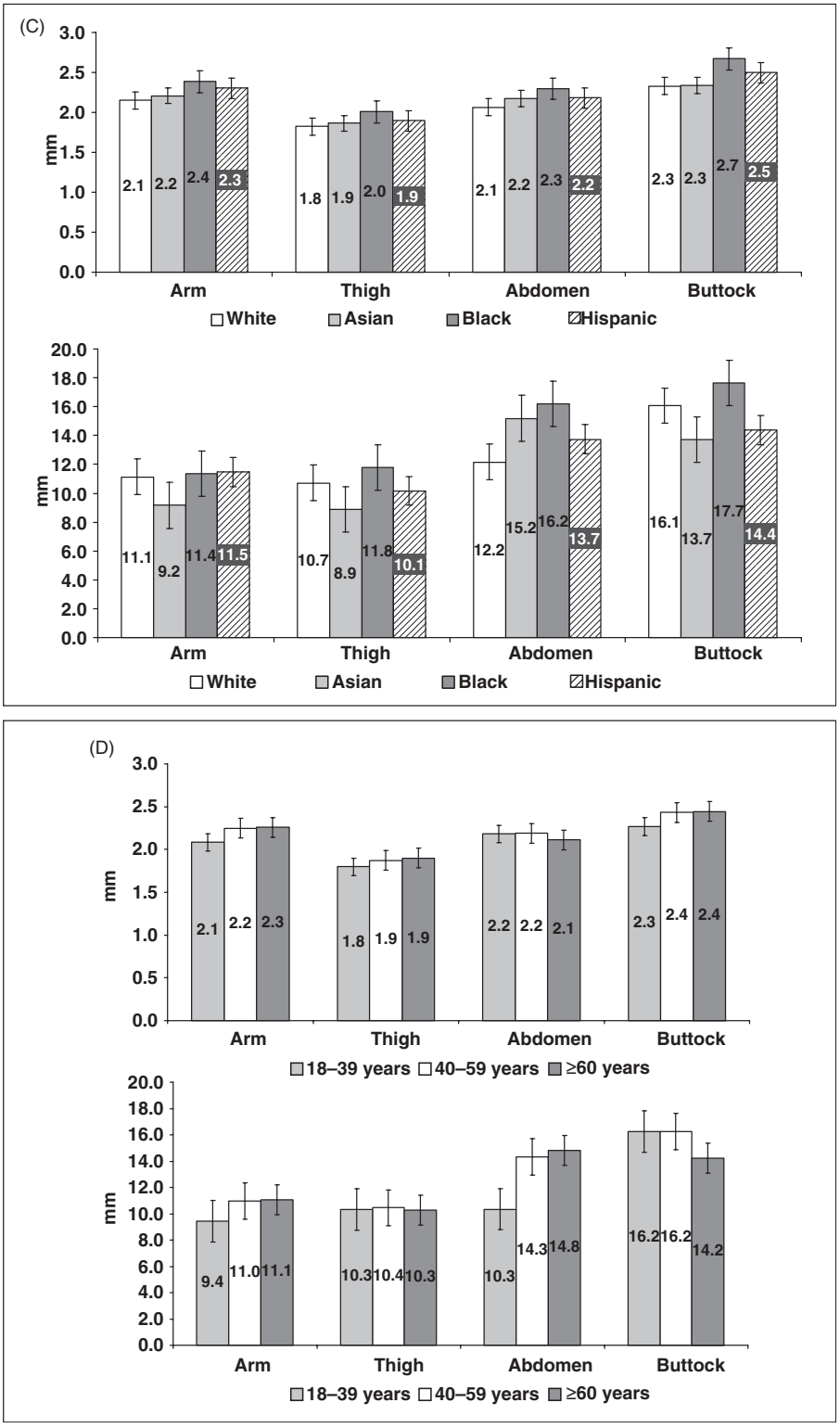

Figure 3. Continued.

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0.2 mm change in ST). Similarly, race, age, and type of diabetes had little clinically important effect on ST. Males do have thicker skin than women – but by only 0.3 mm, on average. We could not confirm a common assumption that older persons have 'thin' skin. The usual sites for insulin injection have variable degrees of exposure to sunlight – some prior reports indicate changes in cutaneous echogenicity depending on dermal photo aging[25,26], but the current findings show little if any change in ST with subjects' aging[17,18,27]. On the other side of the age spectrum, these data may support the conclusion of a previous pediatric study that showed ST in children was slightly thinner than adults: ST in the upper abdomen increased from 1.28 to 1.63 mm from ages 2–13 vs. 2.01 mm in adults aged 25–40[28].

Table 5. Subcutaneous thickness (mm) by body site.

Site	*n*	Mean	SD	95% CI
Arm	382	10.77	5.62	10.21, 11.33
Thigh	387	10.35	5.65	9.79, 10.92
Abdomen	371	13.92	7.26	13.18, 14.66
Buttock	369	15.45	7.27	14.70, 16.19

n, number of subjects; SD, standard deviation; CI, confidence interval.

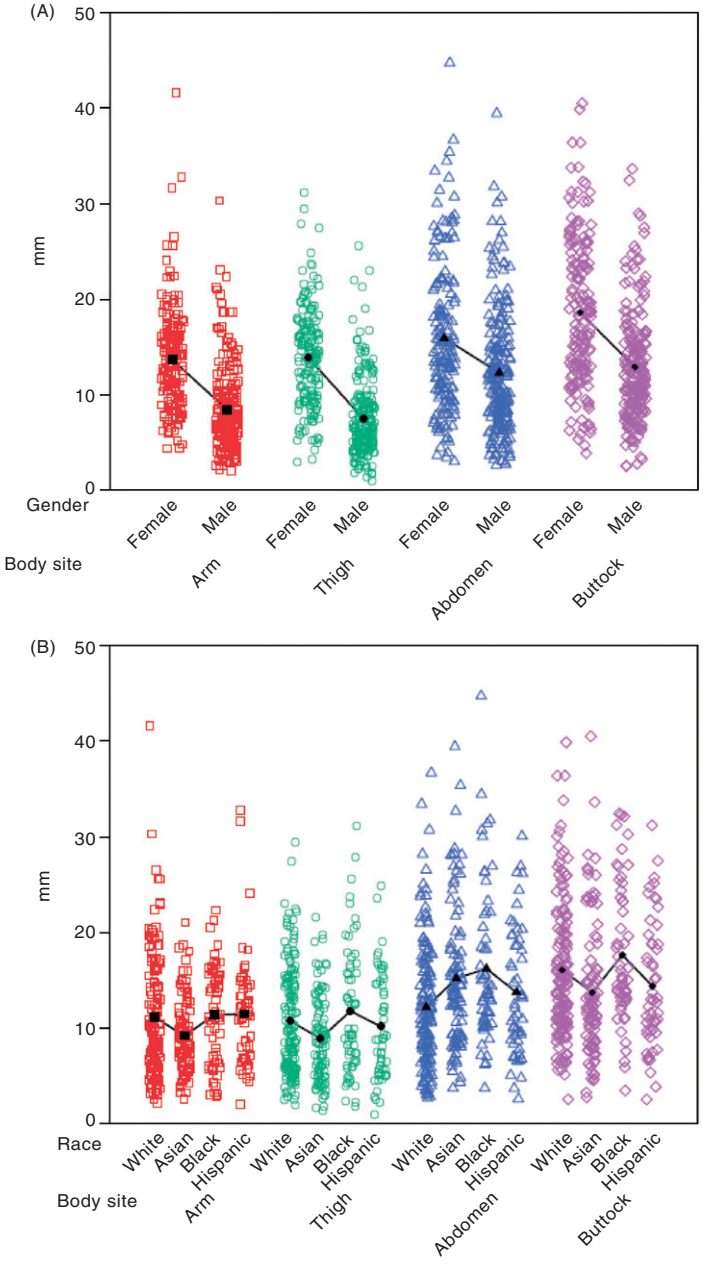

Figure 4. All data points of subcutaneous thickness for all subjects at all four injection sites. (A): Data shown according to gender. (B): Data shown according to race. Black line connects the means within each injection site.

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Table 6. Needle length and calculated injection tissue depth.

	90° insertion			45° insertion		
	ID	SC	IM	ID	SC	IM
Needle length						
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

mm, millimeter; ID, intradermal; SC, subcutaneous; IM, intramuscular. Paired skin and subcutaneous measurements were combined to calculate the distance from the skin surface to the muscle fascia. Assuming either a 45° or 90° needle insertion, without compressing the skin, the anatomical location where medication would be delivered was estimated. No injections were performed.

These measurements indicate much greater variability in SCT than of ST. The 95% CI margins for mean SCT at all four sites varied from approximately 9.8 mm (lower bound) in the thigh to 16.2 mm (upper bound) in the buttocks. As expected, SCT was directly related to BMI – a change of 10 BMI units accounted for approximately 4 mm change in SCT. Females have greater SCT than males by ~5 mm, as has been previously reported[16,19,29–31]. Body site relates to SCT, with the buttocks the thickest.

By combining the measurements of ST and SCT, estimates were made of the depth of drug delivery with needles of varying length inserted without raising a skin fold – shown in Table 6. These calculations assume either a 90° or 45° insertion of the full needle length, without skin depression. From the 1208 *pairs* of ST and SCT measurements in all participants at all four injection sites, the numbers of injections were calculated that would deliver drug into the subcutaneous space, as well as either into the skin (intra-dermal) or into the muscle. It is estimated that >98% of 90° insertions with a 5 mm needle will be in the SC tissue, with the remainder being IM. Needles of 6 mm and 8 mm length have proportionately more injections into muscle (>5% and 15%, respectively). A 12.7 mm (½ inch) needle inserted at 90° will be IM 45% of the time, and even with a 45° injection angle, will still be in the muscle for 21% of injections. These data support the movement of the field to shorter needle lengths. The authors recognize that these estimates do not account for slightly angled insertions, nor small amounts of adhesive mounting material at the base of the needle cannula that may decrease effective needle length, but should be of great assistance for needle length recommendations.

The study data indicate that an even shorter-length, 4 mm needle will successfully deliver medication subcutaneously at all sites in nearly all adults with diabetes. Specifically, it is estimated that perpendicular insertion of such needles will deliver drug into the SC space >99.5% of the time, without intradermal injections. A randomized controlled study evaluating such injections with a new 32 gauge, 4 mm insulin pen needle has just been completed in diabetic subjects, and the results presented in the accompanying paper by Hirsch *et al.*[32].

The additional MRI study supports the calculated injection results, above. Figure 5 shows precise anatomic deposition of small volume (40 µL) saline injections into the thigh of a healthy adult male, using 90° insertions of pen needles 4–8 mm in length. Both the 4 mm and 5 mm pen needles deposit the saline within the SC tissue, whereas the 6 mm injection is at the level of the muscle fascia, and the 8 mm injection clearly lies within the muscle tissue. Results would likely differ in patients with lower or higher BMI.

Many clinicians believe that shorter needles are inappropriate for patients who are obese, and advise using 8 mm or even 12.7 mm needles to deliver SC medication fully. Nearly 2 decades ago, Frid and Linde found no difference in absorption of iodine-125 labeled regular insulin injected at deep and superficial subcutaneous levels, in either the abdomen or the thigh[31]. Two recent crossover studies demonstrate clear equivalence of glycemic control in obese patients when using shorter-length needles: There was no significant difference in HbA1c comparing 29G, 12.7 mm to 31G, 6 mm pen needles[18], or 31G, 5 mm to 31G, 8 mm needles[33]. In obese people who inject insulin, shorter needles are just as effective in maintaining similar glycemic control as longer needles, without adverse effects, and are generally preferred by the patients. Similar findings were reported when 5 mm pen needles were first introduced and compared to 8 mm needles in pediatric and adult studies[34].

Limitations

Limitations of this study are that it measured only adults, and only in the US. However, the size and diversity of the population studied should permit generalizing these findings to nearly all adults with diabetes. Pediatric patients with diabetes may require additional studies. There were differences in the demographic characteristics of the four racial/ethnic groups, and between the type 1 and type 2 diabetes subgroups. However, the multivariate analyses provide a reasonable estimate of the impact of different demographic factors on ST and SCT. Some measurements could not be properly evaluated by the scan reader, especially for ST in the buttocks. The thickness of the SCT in some morbidly obese subjects may have been under-estimated. The maximum SCT obtained was <50 mm, which may reflect limitations of the ultrasound probes used – further study may be warranted. A non-diabetic control group was not included, so inferences about possible

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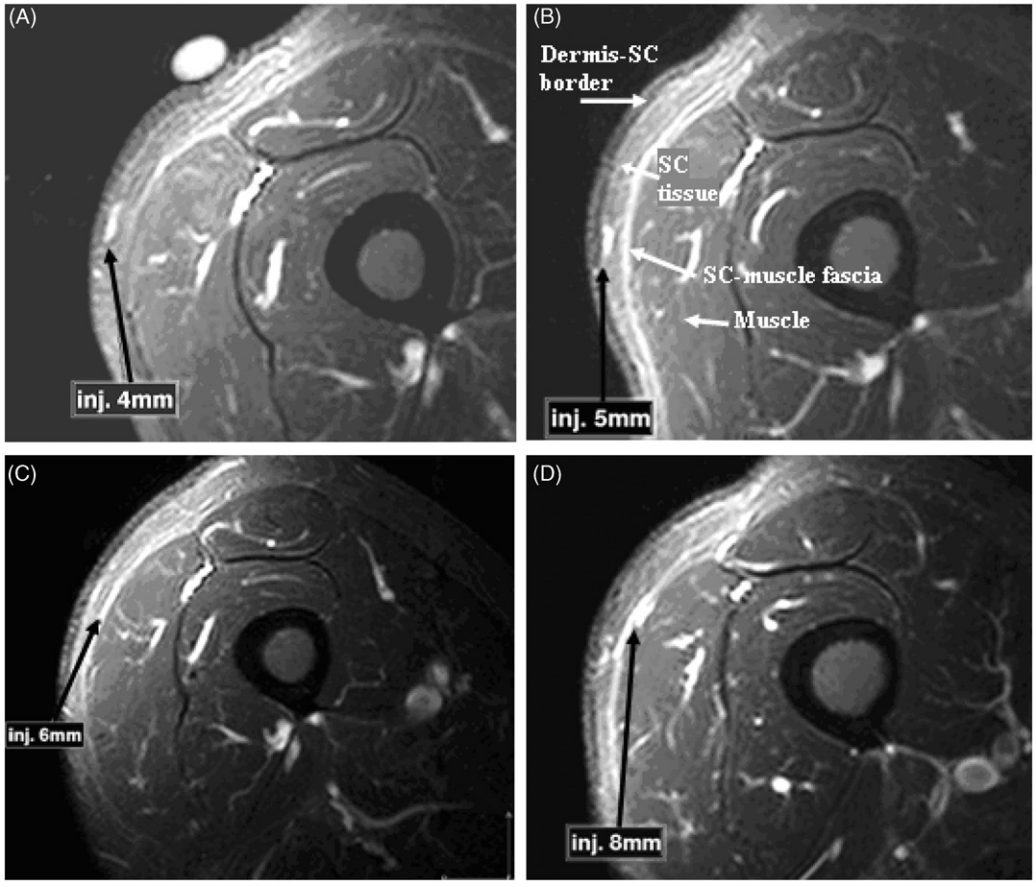

Figure 5. Anatomic localization of injections with different length pen needles. 40 μl (4 'units') of saline were injected into the upper, outer middle part of the right thigh of a healthy adult male with BMI 25.2 kg/m^2. Needles were inserted at 90° up to the hub of the pen needle, without lifting a skin fold. The injection deposits are seen as the high-intensity white reflections in each image. (A) 4 mm (B) 5 mm (C) 6 mm (D) 8 mm. The 4 mm and 5 mm injections are located within the subcutaneous adipose tissue; the 6 mm injection is at the SC-muscle fascia; the 8 mm injection is in the superficial muscle tissue. Used with permission from Drs B. Lindén and A. Frid.

differences of ST and SCT in diabetics compared to normal adults rely on comparisons to other published studies.

Conclusion

These findings are of practical importance to clinicians, educators, patients, injection drug developers and researchers. Knowing that skin thickness varies minimally between patient groups of differing demographics and is rarely >3 mm provides strong assurance that needles shorter than 8 mm length will consistently deliver medications beyond the skin into the subcutaneous adipose layer. In fact, 5 mm and even 4 mm needles are estimated to provide reliable subcutaneous drug delivery, with substantially reduced risk of IM injection – confirmed with MRI imaging. These data can be used for optimal needle length selection and patient injection technique training so insulin injections can be performed with greater reliability and consistency.

Transparency

Declaration of funding

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Declaration of financial/other relationships

M.A.G., C.H.A., K.J.B., and L.J.H. have disclosed that they are employees of BD. K.J.B. has disclosed that she owns stock in several companies, all outside the healthcare industry. L.J.H. has disclosed that he owns stock in BD and Merck. M.A.G. has disclosed that he owns stock in BD.

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References

1. Kolendorf K, Bojsen J, Deekert T. Clinical factors influencing the absorption of 125 I-NPH insulin in diabetic patients. Horm Metab Res 1983;15:274-8
2. Thow JC, Johnson AB, Fulcher G, et al. Different absorption of isophane (NPH) insulin from subcutaneous and intramuscular sites suggests a need to reassess recommended insulin injection technique. Diabet Med 1990;7:600-2
3. Thow JC, Home PD. Insulin injection technique: depth of injection is important. Br Med J 1990;301:3-4
4. Engstrom L. Technique of insulin injection: is it important? Pract Diab 1994;11:39
5. Strauss K, De Gols H, Letondeur C, et al. The Second Injection Technique Event (SITE), May 2000, Barcelona Spain). Pract Diab Int 2002;19:17-21
6. Matsumura M, Monden Y, Nakatani T, et al. Improvement of glycemic control by reeducation in insulin injection technique. Diabetes 2007;56(S1): Abstract 0157-OR
7. Vaag A, Pedersen KD, Lauritzen M, et al. Intramuscular verse subcutaneous injection of unmodified insulin: consequences for blood glucose control in patients with type 1 diabetes mellitus. Diab Med 1990;7:335-42
8. Owens DR, Coates PA, Luzio SD, et al. Pharmacokinetics of 125I-labeled insulin glargine (HOE 901) in healthy men: comparison with NPH insulin and the influence of different subcutaneous injection sites. Diabetes Care 2000;23:813-19
9. Clauson PG, Linde B. Absorption of rapid-acting insulin in obese and non-obese NIDDM patients. Diabetes Care 1995;18:986-91
10. Hildebrandt P, Sestoft L, Nielsen SL. The absorption of subcutaneously injected short-acting soluble insulin: influence of injection technique and concentration. Diabetes Care 1983;6:459-62
11. Heinemann L. Variability of insulin absorption and insulin action. Diab Technol Ther 2002;4:673-82
12. Frid A, Gunnarsson R, Güntner P, et al. Effects of accidental intramuscular injection on insulin absorption in IDDM. Diabetes Care 1988;11:41-5
13. Polak M, Beregszaszi M, Belarbi Ni, et al. Subcutaneous or intramuscular injections of insulin in children. Are we injecting where we think we are? Diabetes Care 1996;19:1434-6
14. Frid A, Lindén B. Where do lean diabetics inject their insulin? A study using computed tomography. Br Med J (Clin Res Ed) 1986;292:1638
15. Vaag A, Handberg A, Lauritzen M, et al. Variation in absorption of NPH insulin due to intramuscular injection. Diabetes Care 1990;13:74-6
16. Tubiana-Rufi N, Belarbi N, Du Pasquier-Fediaevsky L, et al. Short needles (8 mm) reduce the risk of intramuscular injections in children with type 1 diabetes. Diabetes Care 1999;22:1621-5
17. Laurent A, Mistretta F, Bottigioli D, et al. Echographic measurement of skin thickness in adults by high frequency ultrasound to assess the appropriate microneedle length for intradermal delivery of vaccines. Vaccine 2007; 25:6423-30
18. Schwartz S, Hassman D, Shelmet J, et al. A multicenter, open-label, 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; 26:1663-78
19. Hofman PL, Lawton SA, Peart JM, et al. An angled insertion technique using 6-mm needles markedly reduces the risk of intramuscular injections in children and adolescents. Diabet Med 2007;24:1400-5
20. Birkebaek NH, Solvig J, Hansen B, et al. A 4-mm needle reduces the risk of intramuscular injections without increasing backflow to skin surface in lean diabetic children and adults. Diabetes Care 2008;31:e65; doi:10.2337/dc08-0977
21. Nordander C, Willner J, Hansson G. Skerfving influence of the subcutaneous fat layer, as measured by ultrasound, skinfold calipers and BMI, on the EMG amplitude. Eur J Appl Physiol 2003;89:514-19
22. Poland GA, Borrud A, Jacobson RM, et al. Determination of deltoid fat pad thickness, implications for needle length in adult immunization. JAMA 1997;277:1709-11
23. Cash CJC, Berman LH, Treece GM, et al. Two- and three-dimensional ultrasound in the development of a needle-free injection system. Br J Radiol 2004;77:236-42
24. Schou AJ, Thomsen K, Plomgaard AM, et al. Methodological aspects of high-frequency ultrasound of skin in children. Skin Res Technol 2004;10:200-6
25. Gniadecka M. Effects of ageing on dermal echogenicity. Skin Res Technol 2001;7:204-7
26. Smith L. Histologic characteristics and ultrastructure of ageing skin. Cutis 1989;43:414-24
27. Gniedecka M, Jemec GBE. Quantitative evaluation of chronological ageing and photo ageing *in vivo*: studies on skin echogenicity and thickness. Br J Derm 1998;139:815-21
28. Seidenari S, Giusti G, Bertoni L, et al. Thickness and echogenicity of the skin in children as assessed by 20-MHz ultrasound. Dermatology 2000;201:218-22
29. Burbridge BE. Computed tomographic measurement of gluteal subcutaneous fat thickness in reference to failure of gluteal intramuscular injections. Can Assoc Radiol J 2007;58:72-5
30. Birkebaek NH, Johansen A, Slovig J. Cutis/subcutis thickness at insulin injection sites and localization of simulated insulin boluses in children with type 1 diabetes mellitus: need for individualization of injection technique? Diabet Med 1998;15:965-71
31. Frid A, Linde B. Intraregional differences in the absorption of unmodified insulin from the abdominal wall. Diabet Med 1992;9:236-9
32. Hirsch LJ, Klaff LJ, Bailey TS, et al. Comparative glycemic control, safety and patient ratings for a new 4 mm x 32G insulin pen needle in adults with diabetes. Curr Med Res Opin 2010;26:1531-41
33. Kreugel G, Keers JC, Jongbloed A, et al. The influence of needle length on glycemic control and patient preference in obese diabetic patients. Diabetes 2009;58(S1): Abstract 440-P
34. Strauss K, Hannet I, McGonigle J, et al. Ultra-short (5 mm) insulin needles: trial results and clinical recommendations. Pract Diab Int 1999;16:218-22

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