Worldwide Injection Technique Study: Injecting Complications

Introduction

In two previous papers we introduced the worldwide Injection Technique Questionnaire (ITQ) survey patient population [1] and injecting practice [2]. In conjunction with the results, we gave best practice recommendations which are evidence-based. We propose to continue this expose, using the same approach, for Injecting Complications.

Methods and Materials

Our previous paper[3] described the methods, materials, centers and patients who participated in the study.

Results

Lipohypertrophy (LH)

Patients were asked: *Do you have any swelling or lumps under the skin at your usual injection sites that have been there for some time (weeks, months or years)?*

Answer	N	%
Yes	3855	**29.0**
No	9334	**70.2**

Nurses were asked to examine all the patient's injection sites both visually and by palpation and to report any LH.

SITE	EXAM TYPE	% lipos found
ABDOMEN	Visual	**17.3**
	Palpation	**21.1**
THIGH	Visual	**9.8**

[1] Worldwide Injection Technique Study: Population Surveyed 2015.
[2] Worldwide Injection Technique Study: Injecting Practices 2015.
[3] Worldwide Injection Technique Study: Population Surveyed 2015.

	Palpation	**11.2**
BUTTOCKS	Visual	**2.1**
	Palpation	**2.8**
ARM	Visual	**11.2**
	Palpation	**13.4**

Overall, the nurse found lipohypertrophy in 30.8% of patients. Hence we see that that LH is present in nearly 1/3 of survey subjects worldwide. Its frequency is relatively consistent across the 42 countries surveyed. LH is seen almost twice as frequently in T1DM than in T2DM and is virtually absent in GDM, presumably because of the very short time injecting insulin. Although there was a correlation between lesions that were visible and those that were palpated, it was not 100%. The following table presents data on abdominal LH (the most frequently seen).

		Visible	
		No	**Yes**
Palpable	**No**	5112	23
	%	97.1%	.4%
	Yes	186	1102
	%	13.0%	76.8%

Almost 77% of LH could be both seen and felt, but 13% could be felt but not seen. Only 0.4% could be seen but not felt. The same pattern is seen with the thigh, buttocks and arm (data not shown). When nurses found LH they were asked to measure along its longest dimension in mm.

SIZE LH (in mm)	N	**Mean**	SD	Minimum	Maximum
ABDOMEN	1320	**44.5**	36.1	2	300
THIGH	487	**41.9**	36.9	10	300
BUTTOCKS	54	**49.7**	52.7	10	350
ARM	393	**35.7**	26.5	2	300

When nurses found LH they asked the patient if they were still injecting into it and 44.0% said yes. They were then asked how often.

Frequency	%
Every injection	**16.7**
Frequently (daily)	**39.5**
Occasionally (weekly)	**30.3**
Seldom (monthly)	**13.5**

Patients who injected into LH were asked why they did so.

Reason	%
It's convenient	**11.3**
It's less painful	**16.8**
Just a habit	**30.8**
Don't know	**28.0**

Associations: LH is associated with giving more injections per day, with an earlier age of diagnosis of DM (especially in T1DM), with a longer number of years with DM and with a longer number of years on insulin. However there is no association between the presence of LH and BMI. There is also not an association between LH and length of time taking GLP1s. Just under 1/3 of those taking GLP1s were found to have LH, but it is unclear if the LH predated the start of the GLP1. The fact that there is no association to the length of time on a GLP1 suggests the LH is not linked to the GLP1. (Data not shown for the above, but all differences were significant to a $p<0.05$.)

Interestingly there is an association between LH and a number of 'sloppy' injection practices, including poor rotation habits, shorter indwell times, injecting through clothing, injecting insulin cold before it has warmed up, using insulins past their expiry dates and inappropriate disposal of used sharps (all with $p<0.05$). It is difficult to assess the significance of these associations, other than to say they are 'fellow travelers'.

Insulin Consumption: There is a strong association between the presence of LH and the total daily dose (TDD) of insulin.

LH	Mean TDD	SD	N
Yes	55.2	33.0	2192
No	45.1	31.5	4889
Total	48.2	32.3	7081

$p < 0.000$

Over 10 IU of insulin on average being consumed in the LH+ population vs LH-. In T2DM patients, this average TDD difference is 13.5 IU. In T1DM patients, the average TDD difference is 5.4 IU. These differences are maintained in the population which continues to inject into LH.

Inject into LH	Mean TDD	SD	N
Yes	56.1	33.2	1644
No	47.1	32.2	2064
Total	51.1	32.9	3708

$p < 0.000$

These differences were seen for different types of insulin: fast-acting analogue (mean of 4.4 IU more), basal analogue (mean of 1.5 IU more) and premix (mean of 9.8 IU more). All currently used families of insulins are associated with the risk of LH. It is difficult to determine if any one type of insulin has higher risks. Even newer analogues show a prevalence of LH in double digits. (Data not shown for the above, but all differences were significant to a $p<0.05$.)

Glucose Control: The presence of LH is associated with higher HbA1c values, an average difference of 0.55.

LH	Mean HbA1c	SD	N
Yes	8.85	2.7	2205
No	8.30	1.9	4795
Total	8.47	2.2	7000

$p < 0.000$

For T1DM the mean increase is 0.54%. For T2DM the mean increase is 0.53%. LH is associated with higher rates of unexplained hypoglycemia and higher rates of glycemic variability as well as more frequent DKA. (Data not shown for the above, but all differences were significant to a $p<0.05$.)

Risk Factors: LH is associated with incorrect rotation of injection sites, using smaller injecting zones, more years on insulin and reusing pen needles. The higher the number of times the pen needle is reused the more frequently reported is the LH.

Times Needle Used	LH	
	Yes	No
2 times	346	675
	33.9%	66.1%
3 – 5 times	463	855
	35.1%	64.9%
6 – 10 times	177	334
	34.6%	65.4%
> 10 times	195	250
	43.8%	56.2%
TOTAL	1181	2114
	35.8%	64.2%

$p < 0.000$

The size of the LH is also related to the number of times the needle is used.

	Mean Diameter Thigh LH (mm)	SD	N
2 times	**34.6**	25.5	65
3 – 5 times	**42.5**	34.9	112
6 – 10 times	**45.3**	41.7	43
> 10 times	**54.8**	53.4	32
TOTAL	**42.5**	37.2	252

$p < 0.000$

By Logical Regression analysis, incorrect rotation and years on insulin are the most important factors associated with LH ($p<0.001$), while pen needle reuse is significantly, but slightly less strongly associated ($p=0.023$).

Rotation of Injecting Sites

Nearly 5 out of 6 injectors claim to rotate injection sites. Of these, 2/3 were found by nurses to be rotating correctly. **Correct site rotation** is defined as always injecting at least 1 cm from a previous injection. Those who rotate correctly tend to have less

hyperglycemia, less LH, less unexplained hyperglycemia and less glucose variability. (Data not shown for the above, but all differences were significant to a $p<0.05$.) HbA1c is lower in those who correctly rotate by an average of 0.53.

Correct Rotation	Mean HbA1c	SD	N
Yes	8.28	1.787	5187
No	8.85	2.012	2123
Total	8.44	1.873	7310

$p < 0.000$

By Linear Regression analysis, incorrect rotation and years on insulin are the most important factors associated with LH ($p<0.001$), while pen needle reuse is significantly, but slightly less strongly associated ($p=0.023$). HbA1c values are approximately 0.5 higher in injectors with LH (in both T1DM and T2DM) and are significantly higher with incorrect rotation of sites. The frequency of unexpected hypoglycemia and glucose variability are significantly higher with LH, with injecting into LH and with incorrect rotation of sites.

Correct rotation is also associated with lower TDD by an average of 4.7 IU.

Correct rotation	Mean TDD	SD	N
Yes	47.2	31.8	5220
No	51.9	33.1	2164
Total	48.6	32.3	7384

$p < 0.000$

Checking sites routinely is associated with lower HbA1c levels, less LH and more correct rotation. Patients are also more likely to rotate correctly if they have received injection instruction in the last 6 months. Lower TDD of insulin is associated with correct rotation of injections. Correct rotation seems to increase in frequency as the needle shortens, although this may be a byproduct of the level of education and training given when switching patients to such needles.

	Needle Length			
	4	8	6	8

Correct Rotation	**Yes**	1625	1084	1084	1290
	%	76.3%	71.1%	71.6%	63.9%
	No	504	440	430	728
	%	23.7%	28.9%	28.4%	36.1%

$p < 0.000$

Correct rotation also seems to increase as the gauge thins and as the site inspection and injection training become more routine. (Data not shown for the above, but all differences were significant to a $p<0.05$.)

Bleeding and Bruising

Patients were asked if they saw bleeding or bruising from their injection sites and 60.2% said they did. They were also asked about the frequency and only 0.5% said it was 'always', 7.3% said 'often' (several times a week), 41.5% said 'sometimes' (several times a month) and 50.8% said it was 'almost never' (several times a year).

Pain

Our results showed that just over half of injectors report having pain on injection. Of these, 4 out of 5 report having painful injections only several times a month or year (i.e. not with every injection). Groups with higher frequency of reported pain are: T1DM patients, children, adolescents and women. Pain seems also to be commonly associated with bleeding.

		Pain	
		Yes	**No**
Bleeding	**Yes**	3836	1607
	%	70.5%	29.5%
	No	1196	2422
	%	33.1%	66.9%

$p < 0.000$

Pain is also associated with several other disorders, without obvious causative relationship: injecting through clothes, using cold insulin, skipping injections, hypo- and hyperglycemia, LH, injecting into LH, incorrect site rotation, higher HbA1c, lower BMI, younger age and higher TDD. (Data not shown for the above, but all differences were significant to a $p<0.05$.) Pain is also associated with needle reuse and seems to increase as a function of the number of times the needle is reused.

		Pain	
		Yes	No
Number of times Needle Used	2	588	534
	%	52.4%	47.6%
	3-5	863	704
	%	55.1%	44.9%
	6-10	362	246
	%	59.5%	40.5%
	>10	298	176
	%	62.9%	37.1%

$p < 0.000$

Lipoatrophy and Inflammation

Nurses also examined each injection site for the presence of lipoatrophy and redness.

SITE	FINDING	%
ABDOMEN	Lipoatrophy	**0.6**
	Redness	**3.3**
THIGH	Lipoatrophy	**0.5**
	Redness	**2.8**
BUTTOCKS	Lipoatrophy	**0.2**
	Redness	**0.4**
ARM	Lipoatrophy	**0.4**
	Redness	**3.6**

Insulin Leakage

Just over 1/3 of patients report leakage of insulin from the skin. Of these, 5 out of 6 say it occurs rarely (several times a month or a year). Leakage occurs more frequently in T1DM patients than T2DM. Leakage appears to be more frequent if patients have LH or inject into LH, do not leave the pen needle under the skin for 10 seconds after injecting or do not rotate injections correctly.

Dwell Times	Leakage		Total
	Yes	No	
< 5 sec	649	936	1585
	40.9%	59.1%	100.0%
5–10 sec	1512	2394	3906
	38.7%	61.3%	100.0%
> 10 sec	974	1751	2725
	35.7%	64.3%	100.0%
Not aware how long	142	189	331
	42.9%	57.1%	100.0%

$p < 0.000$

The longer pen users leave the needle under the skin after the plunger is pushed in (and especially if they reach the 10-second goal) the less leakage is reported. Of patients who weren't aware how long they left the needle in, almost half had leakage. Leakage is associated with pain, bleeding, hypo- and hyperglycemia, unexplained hypoglycemia and glucose variability. Leakage is not associated with needle reuse, the type of insulin used, lifting a skin fold, the angle of insertion or BMI. Patients with leakage had slightly higher HbA1c and used on average 5.2 IU more of insulin a day.

Leakage	TDD	SD	N
Yes	51.8	32.2	2819
No	46.6	32.5	4777
Total	48.5	32.4	7596

$p < 0.000$

Discussion

Lipohypertrophy (LH)

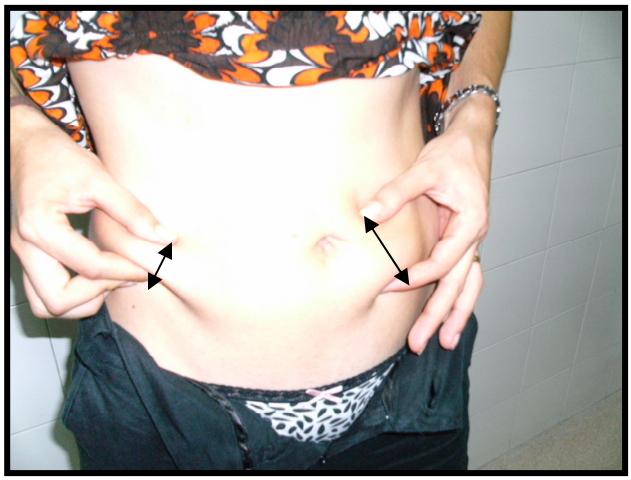
LH is a thickened, 'rubbery' lesion that appears in the SC tissue of injecting sites in up to half of patients who inject insulin. In some patients the lesions can be hard or scar-like. [4] [5] Detection of LH requires both visualization and palpation of injecting sites, as some lesions can be more easily felt than seen. [6] Making two ink marks at opposite edges of the LH (at the junctions between normal and 'rubbery' tissue) will allow the lesion to be measured, recorded, and followed long-term.

More than a third of our participants described lesions consistent with LH at their injection sites and approximately the same proportion were found to have LH by the examining nurse (using visual inspection and palpation) at the time of the ITQ. Figure 3 illustrates visible LH in a woman who had injected in the same two locations below the umbilicus for twelve years. Figure 4 illustrates the detection of palpable LH by comparing a fold of normal skin (arrow tips close together) with lipohypertrophic tissue (arrow tips spread apart). Normal skin can be pinched tightly together, while lipohypertrophic lesions cannot. [7]

Figure 3: Two visible lipohypertrophic lesions below the umbilicus

[4] Thow JC, Johnson AB, Marsden S, Taylor R, Home PH. Morphology of palpably abnormal injection sites and effects on absorption of isophane (NPH) insulin. Diabetic Medicine 1990;7:795-799.
[5] Richardson T, Kerr D. Skin-related complications of insulin therapy: epidemiology and emerging management strategies. American J Clinical Dermatol 2003;4:661-667.
[6] Seyoum B, Abdulkadir J. Systematic inspection of insulin injection sites for local complications related to incorrect injection technique. Trop Doct 1996;26:159-161.
[7] Photographs courtesy of Lourdes Saez-de Ibarra and Ruth Gaspar, Diabetes Nurses and Specialist Educators from La Paz Hospital, Madrid, Spain.

Figure 4: The different 'pinch' characteristics of normal (left) versus lipohypertrophic (right) tissue.



The prevalence rates of LH amongst insulin-injecting patients with DM in five recent studies are, from lowest to highest: 14.5% (Hajheydari, 2008[8]); 27.1% (Raile, 2001[9]); 34.5% (Partanen, 2000[10]); 48.0% (Kordonuri, 2002[11]); 64% (Blanco, 2013[12]). Vardar [13] found that the prevalence of LH at insulin injections sites was 48.8% in 215 Turkish patients who had been using insulin for at least 2 years; Seyoum [14] found LH in 31% of 100 insulin injectors in Ethiopia; and Hauner [15] reported that 28.7% of the 233 German patients studied with T1DM had the condition. In the 2010 Injection Technique Questionnaire (ITQ) Survey [16] 48% of the over 4200 patients insulin answered Yes to the following question (acknowledged to be somewhat non-specific), 'Have you ever noticed swelling of fatty tissue or small bumps at your injection sites?' The percentages in all 16 countries surveyed were all in double digits and ranged from 30 to 88%. A number of earlier surveys [17] [18] [19] [20] have reported similar findings.

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[8] Hajheydari Z, Kashi Z, Akha O, Akbarzadeh S. Frequency of lipodystrophy induced by recombinant human insulin. Eur Rev Med Pharmacol Sci. 2011 Oct;15(10):1196-201.

[9] Raile K, Noelle V, Landgraf R, Schwarz HP. Insulin antibodies are associated with lipoatrophy but also with lipohypertrophy in children and adolescents with type 1 diabetes. Exp Clin Endocrinol Diabetes. 2001;109(8):393-6.

[10] Partanen TM, Rissanen A. Insulin injection practices, Pract Diab Int 2000;17:252-4.

[11] Kordonouri O, Lauterborn R, Deiss D. Lipohypertrophy in young patients with type 1 diabetes. Diabetes Care. 2002 Mar;25(3):634.

[12] Blanco M, Hernández MT, Strauss KW, Amaya M. Prevalence and risk factors of lipohypertrophy in insulin-injecting patients with diabetes. Diabetes Metab. 2013 Oct;39(5):445-53.

[13] Vardar B, Kizilci S. Incidence of lipohypertrophy in diabetic patients and a study of influencing factors. Diabetes Res Clin Pract 2007;77:231-6.

[14] Seyoum B, Abdulkadir J. Systematic inspection of insulin injection sites for local complications related to incorrect injection technique. Trop Doct 1996;26:159-161.

[15] Hauner H, Stockamp B, Haastert B. Prevalence of lipohypertrophy in insulin-treated diabetic patients and predisposing factors. *Exp Clin Endocrinol Diabetes* 1996;104:106-10.

[16] De Coninck C, Frid A, Gaspar R, et al. Results and analysis of the 2008-2009 Insulin Injection Technique Questionnaire survey. J Diabetes. 2010 Sep;2(3):168-79.

[17] Strauss K, Insulin injection techniques: Report from the 1st International Insulin Injection Technique Workshop, Strasbourg, France—June 1997, Pract Diab Int 1998;15:16-20.

Blanco[21] studied 430 patients from 19 Spanish centers and found that nearly 2/3 (64.4%) had LH. It was more commonly in T1DM (72.3%) than in T2DM (53.4%). Grassi[22] studied 388 patients from 18 Italian centers and found a prevalence of 48.7%. In a Chinese study[23] of 401 patients in 4 centers found an overall prevalence of 53.1% (95% CI 48.2, 58.0%). By body site, LH was found in 52.4% of Abdomens examined, 15.5% of thighs and 9.4% of arms.

Lipohypertrophy has also been reported to be frequent in CSII Patients. A cross-sectional study [24] of 50 consecutive patients with T1DM using CSII for >6 months (26 female; age, 13.3 ± 3.5 years; CSII duration, 2.8 ± 1.7 years; HbA1c, 7.7% ± 1.1%) examined the skin for complications associated with therapy. 42% of these patients had LH. A similar survey [25] of 91 adult CSII patients revealed that the commonest infusion site problem was lipohypertrophy (26.1%), which occurred more often in those with long duration of CSII (4.8 [2.38–9.45] vs. 3.0 [1.50–4.25] years; P=0.01).

Vardar [26] also identified, by logistic regression analysis, three independent risk factors for LH: Duration of insulin use, with longer use associated with more LH (p=0.001); Site rotation, with a failure to rotate associated with higher LH risk (p=0.004); Changing needles, with needle reuse also associated with LH (p=0.004). Two other studies [27] [28] have identified similar factors. Immunologic factors in LH are poorly understood, although antibodies seem to have a role in pediatric and adolescent patients with T1DM [29]. Needle length has not been shown to be a risk factor. It is also not known what the impact of different needle lengths is on insulin absorption from injections into LH.

Histopathologically, LH lesions are shown to be entirely formed of adipocytes. These cells are often hypertrophied to two or three times the size of normal adipocytes. They

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[18] Strauss K, De Gols H, Hannet I, Partanen TM, Frid A. A pan-European epidemiologic study of insulin injection technique in patients with diabetes. Pract Diab Int 2002;19:71-76.
[19] Strauss K, De Gols H, Letondeur C, Matyjaszczyk M, Frid A. The second injection technique event (SITE), May 2000, Barcelona, Spain. Pract Diab Int 2002;19:17-21.
[20] Partanen TM, Rissanen A. Insulin injection practices, Pract Diab Int 2000;17:252-4.
[21] Blanco M, Hernández MT, Strauss KW, Amaya M. Prevalence and risk factors of lipohypertrophy in insulin-injecting patients with diabetes. Diabetes Metab. 2013 Oct;39(5):445-53.
[22] G. Grassi, Scuntero P, Trepiccioni R, et al. Optimizing insulin injection technique and its effect on blood glucose control. Journal of Clinical & Translational Endocrinology 1 (2014): 145-150. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/3.0/).
[23] Ji L, Li Q, Wei G. Lipohypertrophy - prevalence, risk factors and clinical characteristics of insulin-requiring patients in China. Abstract, EASD Vienna 2014, Tracking Number: A-14-747.
[24] Conwell LS, Pope E, Artiles AM, Mohanta A, Daneman A, Daneman D. Dermatological complications of continuous subcutaneous insulin infusion in children and adolescents. *J Pediatr*. 2008;152:622-628.
[25] Pickup J, Yemane N, Brackenridge A, Pender S. Nonmetabolic Complications of Continuous Subcutaneous Insulin Infusion: A Patient Survey. Diabetes Technology & Therapeutics 2014; 16:145-9.
[26] Vardar B, Kizilci S. Incidence of lipohypertrophy in diabetic patients and a study of influencing factors. Diabetes Res Clin Pract 2007;77:231-6.
[27] Blanco M, Hernández MT, Strauss KW, Amaya M. Prevalence and risk factors of lipohypertrophy in insulin-injecting patients with diabetes. Diabetes Metab. 2013 Oct;39(5):445-53.
[28] Saez-de Ibarra L, Gallego F. Factors related to lipohypertrophy in insulin-treated diabetic patients; role of educational intervention. Pract Diab Int 1998;15:9-11.
[29] Raile K, Noelle V, Landgraf R, Schwarz HP. Insulin antibodies are associated with lipoatrophy but also with lipohypertrophy in children and adolescents with type 1 diabetes. Exp Clin Endocrinol Diabetes. 2001;109(8):393–6.

can be seen invading the adjacent reticular dermis, engulfing lipid droplets, proliferating or manifesting other signs of metabolic activation [30]. This anabolic activity is presumably initiated by trauma from repeat injections in the same place and time coupled with the growth-promoting properties of insulin. There may be genetic factors but these have not yet been elucidated.

Almost all studies of patients injecting into LH [31] [32] [33] [34] show insulin absorption to be delayed or erratic, potentially worsening diabetes management.
Franzen [35] evaluated children with diabetes who were injecting into clinically detectable LH. The children received simple but direct instructions: Rotate injection sites; and Do not reuse your needles. In 3 months 90% of LH lesions in these children had resolved and were undetectable. HbA1c was improved significantly and insulin requirements had decreased.

A recent Spanish study entitled Prevalence and Risk Factors of Lipohypertrophy in Insulin - Injecting Patients with Diabetes [36] showed that LH is extremely common, present in 2/3 of patients and is strongly associated with both incorrect rotation of sites of injection and with reuse of needles, especially > 5 times. Unexplained hypoglycemia and glycemic variability were also greatly increased (6 to 7-fold) in those with, Vs those without LH.

The 2014-15 ITQ has shown that approximately 1 out of 4 insulin injectors has unexpected hypoglycemia and more than 1 out of 3 has glucose variability. HbA1c values do not differ between T1DM and T2DM injectors, but T1DM patients have significantly higher frequencies of unexpected hypoglycemia and glucose variability. HbA1c values do not differ amongst the different needle lengths, but injectors using the 6mm needle have somewhat higher frequencies of unexpected hypoglycemia and glucose variability for unknown reasons. HbA1c values are approximately 0.5 higher in injectors with LH (in both T1DM and T2DM) and are significantly higher with incorrect rotation of sites and with needle reuse. HbA1c values are lower in subjects who use larger injection areas and whose sites are inspected routinely. The frequency of unexpected hypoglycemia and glucose variability are significantly higher with LH, with injecting into LH, with incorrect rotation of sites and with needle reuse. Rates of unexpected hypoglycemia and glucose variability are lower when the abdomen is used exclusively as an injection site, but as one adds use of the limbs the rates of both disorders increase.

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[30] Fujikura J, Fujimoto M, Yasue S, et.al. Insulin-induced lipohypertrophy: report of a case with histopathology. Endocr J. 2005 Oct;52(5):623-8.
[31] Young RJ, Hannan WJ, Frier BM, Steel JM, Duncan LJ.. Diabetic lipohypertrophy delays insulin absorption. Diabetes Care 1984;7:479-480.
[32] Chowdhury TA, Escudier V. Poor glycaemic control caused by insulin induced lipohypertrophy. Brit Med J 2003;327:383-384.
[33] Johansson UB. Impaired absorption of insulin aspart from lipohypertrophic injection sites. Diabetes Care 2005;28:2025-7.
[34] Frid A, Linden B. Computed tomography of injection sites in patients with diabetes mellitus. Injection and Absorption of Insulin. Stockholm: Thesis, 1992.
[35] Franzen I, J. Ludvigsson, Linköping 1997 Specific Instructions Gave Reduction of Lipomas and Improved Metabolic Control in Diabetic Children, Diabetologia Vol 40, Supplement 1: A615 (1997).
[36] Blanco M, Hernández MT, Strauss KW, Amaya M. Prevalence and risk factors of lipohypertrophy in insulin-injecting patients with diabetes. Diabetes Metab. 2013 Oct;39(5):445-53.

Getting injection training from a diabetes nurse is associated with significantly lower HbA1c levels as well as less frequent unexpected hypoglycemia and glucose variability.

A critical finding of the above Spanish study is the correlation of total daily dose (TDD) of insulin to the presence of LH and its derived cost to the health care system. Subjects with LH had significantly higher TDD, overall and in both T1DM and T2DM groups. T2DM patients had the highest TDD differences (approximately 20 additional units daily). Such patients tend to have increased weight and insulin resistance compared to T1DM patients, and these factors probably contributed to their greater TDD – however, the T2DM patients with LH had similar weight and BMI as the T2DM without LH. Another major contributor is the practice of injecting into LH where the absorption properties of insulin are distorted. The cost of the additional insulin consumed by injecting into LH was calculated (based on prevalence of LH, number of insulin-injecting patients in Spain, differences in TDD, and the cost in Euros per unit of insulin) to be over 122 million euros in Spain. This is an obvious opportunity for savings to both patients and health care payers. The one weakness of the Spain study is that HbA1c levels were unfortunately not collected on the subjects examined. A Chinese study similar to the Spain one showed remarkably similar results[37], with the addition that patients with LH had significantly higher HbA1c values (8.2 ±1.8) than those without LH (7.7 ±1.5) ($p<0.003$). [38] [39]

The impact of LH on insulin PK-PD is rather poorly documented in the literature. While there are case reports indicating reductions in insulin consumption with improvements in HbA1c when patients with LH were taught to inject into normal areas, and a small number of studies that evaluated insulin PK-PD when patients have injected into areas of LH vs normal areas, the overall quality of such studies is poor and/or they were substantially underpowered. It is assumed that LH reduces and/or slows insulin uptake, and perhaps increases PK-PD variation, but this has not been proven rigorously.

Two closely-related studies have addressed these questions, using state-of-the-art methodologies. A glucose clamp study[40] in patients with LH has shown that both insulin absorption and action are substantially blunted and considerably more variable when

[37]Specifically, LH was present in 52.9% of participants. Patients were an average of 59.6 (SD=11.5) years old and took insulin 5.6 (SD=4.6) years, averaging 33.0 (SD=18.4) U/day. HbA1c was 8.2% (1.8) and 7.7% (1.5), respectively, in those with and without LH ($p=0.003$). LH was associated with higher daily insulin dose (38.1U vs 27.1U, $p<0.001$) and cost (RMB 8.2 vs 5.8, $p<0.001$). Those with LH averaged 2.3 (2.2) nodes, had higher frequency of PN reuse (median 13.0 vs 7.5, $p=0.003$), and greater total 6-month direct costs (RMB 5506.9 vs 5258.0, $p=0.037$). With 8.4 million insulin injectors in China, the estimated *excess* annual direct cost of LH is RMB 2.2 billion ($360 million). Average pain scores (0-10) were higher if LH was present (2.7 vs. 2.0, $p=0.021$), if ≥3 nodes were present (3.8 vs. 2.3, $p<0.001$), and if PNs were not reimbursed (2.8 vs. 1.7, $p<0.001$). Patient satisfaction decreased as presence, number, and size of LH nodes increased (all $p<0.05$).

[38]Ji L, Li Q, Wei G. Lipohypertrophy - prevalence, risk factors and clinical characteristics of insulin-requiring patients in China. Abstract, EASD Vienna 2014, Tracking Number: A-14-747.

[39] Qifu Li, Linong Ji, Zilin Sun, Guijun Qin, Zheng Wei, Junhao Liu, Luan Luan, Laurence Hirsch. Lipohypertrophy (LH) Prevalence Varies Widely Between Chinese Cities - Need For Consistent LH Diagnostic Methods. Abstract submitted to 2015 ADA.

[40] Susanne Famulla, Ulrike Hövelmann, Annelie Fischer, Hans-Veit Coester, Lutz Heinemann, Lars Kaltheuner, Laurence Hirsch, Tim Heise. Lipohypertrophy (LHT) Leads to Blunted, More Variable Insulin Absorption and Action in Patients with Type 1 Diabetes (T1DM). Abstract , 2015 ADA in Boston, USA.

insulin is injected into areas with LH.[41] A separate, mixed meal study in the same subjects confirmed the slower absorption and decreased action of insulin when injected into LH compared to normal adipose tissue, with much greater post-meal glycemic excursions shown. [42]

Site Rotation

Several studies have demonstrated that the best way to safeguard normal tissue is to properly and consistently rotate injecting sites. [43] [44] [45] Injection can be rotated from one body region to another (abdomen to thigh, to buttock, to arm) but it must be remembered that absorption characteristics change depending on the type of insulin given. Analogues can be given at any injection site with similar uptake and action (PK-PD), but human insulins (Regular, NPH) vary substantially – absorption being fastest from the abdomen and from the buttock, slowest. However, correct rotation involves spacing injections a least 1 cm. apart <u>even within</u> an injection zone.

Some clinicians are offering the single-use skin safe marker pen to patients to keep and use to make a dot on the skin where they inject and use this as a reference point for the next injection. This seems to work very well for some patients and the marker from the pen washes off and fades to nothing in about 5 days. One scheme with proven effectiveness involves dividing the injection site into quadrants (or halves when using the thighs or buttocks), using one quadrant per week and moving always clockwise, as shown by figures below. [46]

[41] Specifically the study.investigated insulin exposure and pharmacodynamics of insulin lispro injected into abdominal areas with LH or normal adipose tissue. Thirteen T1DM with LH (confirmed by palpation and ultrasound) received single doses of 0.15 U/kg LIS approximately every 6 hours, twice into a region with LHT and twice into normal tissue. Comparing LHT with NAT injection, LS-mean INS concentrations were comparable during the first 30 min (AUCINS0-0.5h 8.8 vs. 9.4 h*mU/L), but significantly lower thereafter (AUCINS0-1h 29.3 vs. 41.5 h*mU/L, AUCINS.0-4h 97 vs. 154 h*mU/L, all $p<0.02$). Maximum INS exposure was reduced by 34% (CINSmax 49.7 vs. 75.4 mU/L, $p<0.002$). The PD effect in the first 4 h was 27% lower with LHT injection (AUCGIR0-4h: 529 vs. 720 mg/kg, $p<0.05$), whereas maximum GIR was comparable (GIRmax 5.5 vs. 6.0 mg/kg/min, $p=0.378$). Intra-subject variability was substantially higher after dosing into LHT (coefficients of variation 52 vs. 11% [AUCINS.0-4h] and 57 vs. 23%, [AUCGIR0-4h], all $p<0.002$).

[42] Ulrike Hovelmann, Susanne Famulla, Lidia Hermanski, Annelie Fischer, Lutz Heinemannn, Matthias Kaltheuner, Laurence Hirsch, Tim Heise,. Insulin Injection into Regions with Lipohypertrophy (LHT) Worsens Postprandial (PP) Blood Glucose (BG) Versus Injections into Normal Adipose Tissue (NAT). Abstract , 2015 ADA in Boston, USA.

[43] Ahern J, Mazur ML. Site rotation. Diabetes Forecast 2001;54:66-68.

[44] Bantle JP, Weber MS, Rao SM, Chattopadhyay MK, Robertson RP. Rotation of the anatomic regions used for insulin injections day-to-day variability of plasma glucose in type 1 diabetic subjects. JAMA 1990;263:1802-1806.

[45] Davis ED, Chesnaky P. Site rotation...taking insulin. Diabetes Forecast 1992;45:54-56.

[46] Photographs courtesy of Lourdes Saez-de Ibarra and Ruth Gaspar, Diabetes Nurses and Specialist Educators from La Paz Hospital, Madrid, Spain.

Figure 5: Abdominal rotation pattern by quadrants

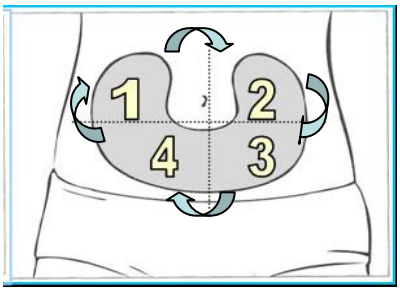
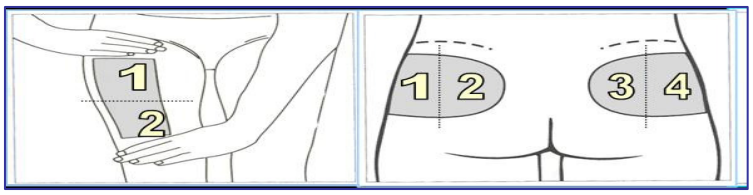


Figure 6: Thigh and Buttocks rotational pattern by halves



Injections within any quadrant or half should be spaced at least 1cm from each other in order to avoid repeat tissue trauma. Pump cannulae should be placed at least 3cm away from previous sites. HCP should verify that the rotation scheme is being followed at each visit and give help and advice where needed.

Lipoatrophy

Lipoatrophy has been reported in all injecting sites. [47] [48] [49] [50] [51] [52] It is now considered a relatively unusual condition, prompting case reporting. Risk factors are not understood. Some authors have suggested young women with other auto-immune disorders may be at

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higher risk. LA is felt to be a local immune reaction against fat cells provoked by insulin crystals. Consequently LA is rarer today than it was when less pure insulins were given. But LA is still observed even with short and long-acting analogues. LA causes significant variability in insulin absorption when injections are given into it.

Treatment for LH is not evidence based due the lack of trials. Several approaches however have been recommended: changing the insulin formulation (e.g., aspart to lispro, or lispro to glulisine, etc.), changing injection sites or shifting to CSII and possibly cortisone injected into the LA. LA may or may not resolve with time, but this depends on the individual patient. LA has been seen with the short-acting analogues, lispro and aspart, as well as the long-acting ones, glargine and detemir. It may also be associated with non-rotation of injection sites and needle reuse. LA is both a cosmetic problem (disfiguring) and a clinical one (erratic and abnormal insulin absorption).

Injection Pain

Most insulin injections are not painful, except in the infrequent event that the needle comes into direct contact with a nerve ending. Some patients, however, are exceptionally sensitive to sensations they describe as painful. Patient awareness of injection discomfort has been studied extensively and is related to three key factors: needle length (and tissue level penetrated); needle diameter; and injection context. Injection context is defined by environment (including noise and the presence of other people), view of the needle and the apprehension of HCPs, both professional and family. The more apprehension the latter display, the greater the pain and anxiety felt by the patient. [53] [54] This reverse transference places a large responsibility on carers to assess their own attitudes towards injection pain. Some patients complain of discomfort when injecting insulins which have a low pH. This seems, anecdotally, to be reported more commonly in children. Glargine is an example of an acidic insulin.

Heise [55] has shown that injection speed (150, 300 and 450 µl/s; equivalent of 15-45 IU/sec of U100 insulin) makes no difference in pain. But injection volume does, with higher volumes (≥1200 µl or 120 IU of U100 insulin) causing more pain. His group also found that injections in the thigh appear to hurt more than those in the abdomen in adults. Anderson[56] and Jorgensen[57] also found that higher injected volumes cause more pain. Hofman[58] as well showed in both children and adults that thigh injections are more

[53] Brady KA, Avner JR, Khine H. Perception and attitude of providers towards pain and anxiety associated with pediatric vaccine injection. Clinical Pediatrics. 50:140-143, 2011.
[54] Diamond S, Matok I. Pharmacists' anticipated pain compared to experienced pain associated with insulin pen injection and fingertip. Canadian Journal of Diabetes. 35:282-286, 2011.
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[56] Anderson G, Meyer D, Herrman CE et al. Tolerability and safety of novel half milliliter formulation of glatiramer acetate for subcutaneous injection: an open-label, multicenter, randomized comparative study. J Neurol 2010; 257:1917–1923.
[57] Jorgensen JT, Romsing J, Rasmussen M, Moller-Sonnergaard J, Vang L, Musaeus L. Pain assessment of subcutaneous injections. Ann Pharmacother 1996;30:729 – 732.
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painful than abdominal. Nevertheless Heise[59] found that most patients say the pain is acceptable regardless of volume or injection site. So we can reasonably conclude that injection pain, though felt under certain circumstances by certain patients, is mild enough to be acceptable to most of them, particularly with today's very thin, short needles.

This ITQ survey showed that just over half of injectors report having pain on injection. Of these, 4 out of 5 report having painful injections only several times a month or year (i.e. not with every injection). Groups with higher frequency of reported pain are: T1DM patients, children, adolescents and women. Pain is associated with several other disorders, without obvious causative relationship: bleeding, injecting through clothes, using cold insulin, skipping injections, hypo- and hyperglycemia, LH, injecting into LH, incorrect site rotation, higher HbA1c, lower BMI, younger age and higher TDD. Pain is also associated with needle reuse and seems to increase as a function of the number of times the needle is reused.

A new set of international injecting recommendations has been developed and is being published. A number of these have been incorporated in the text above. It may be appropriate for the local countries and regions to revise their own guidelines in the light of the new recommendations and the ITQ survey data reported above. This paper will be followed by one other: **Worldwide Injection Technique Study: Education and the Health Care Professional.**

Duality of interest:

Kenneth Strauss is employed by BD, a manufacturer of injecting devices.

Acknowledgments

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[59] Heise T, Nosek L, Dellweg S, et.al. Impact of injection speed and volume on perceived pain during subcutaneous injections into the abdomen and thigh: a single-centre, randomized controlled trial. Diabetes Obes Metab. 2014 Oct;16(10):971-6.