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Original article

Prevalence and risk factors of lipohypertrophy in insulin-injecting patients with diabetes

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Abstract

Introduction. – Our objective was to assess the frequency of lipohypertrophy (LH) and its relationship to site rotation, needle reuse, glucose variability, hypoglycaemia and use of insulin.

Methods. – The study included 430 outpatients injecting insulin who filled out a wide-ranging questionnaire regarding their injection technique. Then, a diabetes nurse examined their injection sites for the presence of LH.

Results. – Nearly two-thirds (64.4%) of patients had LH. There was a strong relationship between the presence of LH and non-rotation of sites, with correct rotation technique having the strongest protective value against LH. Of the patients who correctly rotated sites, only 5% had LH while, of the patients with LH, 98% either did not rotate sites or rotated incorrectly. Also, 39.1% of patients with LH had unexplained hypoglycaemia and 49.1% had glycaemic variability compared with only 5.9% and 6.5%, respectively, in those without LH. LH was also related to needle reuse, with risk increasing significantly when needles were used > 5 times. Total daily insulin doses for patients with and without LH averaged 56 and 41 IU/day, respectively. This 15 IU difference equates to a total annual cost to the Spanish healthcare system of > €122 million. This was also the first study in which the use of ultrasound allowed the description of an "echo signature" for LH.

Conclusion. – Correct injection site rotation appears to be the critical factor in preventing LH, which is associated with reduced glucose variability, hypoglycaemia, insulin consumption and costs.

Keywords: Insulin injection; Lipodystrophy; Lipohypertrophy; Injection rotation; Insulin consumption; Costs

Résumé

Fréquence et facteurs de risques de lipodystrophie chez les patients diabétiques qui s'injectent de l'insuline.

Introduction. – Notre objectif était d'évaluer la fréquence des lipodystrophies (LH) et sa relation avec la rotation des sites d'injection, la réutilisation des aiguilles, la variabilité de glycémie, l'hypoglycémie et la consommation d'insuline.

Méthodes. – L'étude a porté sur 430 patients qui s'injectaient de l'insuline. Ils ont rempli un questionnaire concernant leur technique d'injection et ensuite leurs sites d'injection ont été examinés par une infirmière dans le service de diabétologie pour la présence de LH.

Résultats. – Près de deux tiers des patients (64,4 %) ont eu des LH. Il y avait une forte relation entre la présence de LH et la non-rotation des sites d'injection, une technique de rotation appropriée ayant la plus forte valeur de protection contre la survenue de LH. Chez les patients qui ont fait une rotation correcte, seulement 5 % ont eu des LH. Parmi les patients atteints de LH, 98 % n'ont pas fait de rotation ou l'ont fait de façon inappropriée. Parmi les patients atteints de LH, 39,1 % avaient une hypoglycémie inexpliquée et 49,1 % avaient de la variabilité glycémique ; contre seulement 5,9 % et 6,5 %, respectivement pour ceux qui n'avaient pas de LH. Les LH étaient également liées à la réutilisation de l'aiguille, avec un risque considérablement augmenté lorsque les aiguilles étaient utilisées plus de cinq fois. La dose quotidienne d'insuline chez les sujets avec LH était 56 IU/jour en moyenne contre 41 IU/jour chez les patients sans LH. Cette différence de 15 UI/jour représente un coût total annuel au système de santé espagnol de 122 millions d'euros. Cette étude est la première dans laquelle l'utilisation de l'échographie a permis la description d'une « écho-signature » des LH.

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Conclusions. – La rotation correcte des sites d'injection semble être le facteur déterminant dans la prévention des LH. Éviter les LH est associé avec une réduction de la variabilité des glycémies, moins d'hypoglycémies, une moindre consommation d'insuline et des coûts des traitements plus faibles.

Mots clés : Injection d'insuline ; Lipodystrophie (LH) ; Rotation d'injection ; Consommation d'insuline ; Coûts

1. Introduction

Proper injection technique is essential for optimal functioning of insulin and other injected medications in diabetes [1]. However, healthcare professionals rarely instruct patients adequately on the proper techniques. Rarely do such professionals explain the importance of using a needle length appropriate for the patients' subcutaneous (SC) tissue depth, or train them to rotate sites properly, change needles between injections or monitor their injection sites for the presence of lipodystrophy [2].

Lipodystrophy is one of the most common complications of SC insulin injection and may present as either lipohypertrophy (LH) or lipoatrophy (LA). LH is a thickened 'rubbery' swelling of tissue that is sometimes soft, sometimes firm. Although the exact aetiology of LH is unclear, various local injection-related factors appear to be at play such as the insulin itself with its strong growth-promoting properties, repeated trauma to the same site when patients fail to rotate injections and the repeated use of the same needle [3,4].

In contrast, LA is a scarring lesion due to SC fatty tissue atrophy. Several features of LA suggest an immunological aetiology: it is more frequent in type 1 diabetes (T1D) patients; it affects mostly women, who often have other signs of autoimmunity; mast cells and eosinophils are found in biopsy specimens, and positive responses have been reported to cromolyn therapy (an inhibitor of mast cells) [5]. In LA, there is a lipolytic reaction probably induced by impurities or other components in some insulin preparations, although the prevalence of LA has been falling as insulin has become more purified and now affects only 1–2% of injectors [5].

LH, however, is commonly seen—that is, when sought by examination. Vardar and Kizilci [6] 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 and Abdulkadir [7] found it in 31% of 100 insulin injectors in Ethiopia; and Hauner et al. [8] reported that 28.7% of 233 German T1D patients studied had the condition.

Detection of LH requires both visualization and palpation of injecting sites, as some lesions can be more easily felt than seen [7]. Normal skin can be pinched tightly together whereas LH lesions cannot [9]. Both pen and syringe devices (and all needle lengths and gauges) have been associated with LH, as well as insulin pump cannulae that are inserted repeatedly into the same location [6,10–18].

No randomized prospective studies have been published establishing causative factors in LH. However, published observations support an association between the presence of LH and the use of older, less-purified insulin formulations, failure to rotate sites, small injecting zones, repeatedly injecting the same location and reusing needles [2,10–14]. Most studies suggest that insulin absorption from sites with LH may be delayed or erratic, thereby potentially worsening diabetes management [15–19]. Unpublished data from a trial in Germany (personal communication, Dr Treichel, Magdeburg, 2012) have suggested that, when patients switch injections from LH sites to normal tissue, the dose of insulin required to maintain the same level of glucose control can fall—sometimes dramatically. If this is indeed the case, there are several important implications: first, patients may be at risk of serious hypoglycaemia if they are unaware of the phenomenon when switching to other injection sites; second, it suggests a simple and effective means of reducing glycaemic variability and possibly improving glucose control without increasing insulin doses; and finally, there may be potential cost savings to both patients and the healthcare system due to the reduced use of insulin.

The present study was conducted in a large group of Spanish insulin-injecting patients to assess the frequency of lipodystrophy and to determine the relationship, if any, between such lesions and several key clinical and public-health parameters, including the practice and quality of site rotation, injection frequency, needle length and reuse, and overall patterns of insulin use.

2. Materials and methods

Ours was a multicentre study of outpatients with diabetes treated in primary care (PC) as well as at specialty centres (SpC) in the region of Andalusia, the community of Valencia, and the autonomous cities of Ceuta and Melilla in Spain. Patients were recruited randomly according to the order in which they were seen in the clinic. Study personnel had no knowledge of the lipodystrophy status of patients at study entry, when an assessment of their injection technique was made as well as examination of their injection sites.

The parameters assessed included the patient's needle length, reuse of needles, frequency of hypoglycaemic episodes and presence of glycaemic variability. 'Hypoglycaemia' was defined as the occurrence of one or more symptoms of hypoglycaemia (such as palpitations, tiredness, sweating, strong hunger, dizziness and tremor) and a confirmed blood glucose meter reading of ≤ 60 mg/dL (3.3 mM/L). 'Frequent unexplained hypoglycaemia' was defined as having a hypoglycaemic episode one or more times a week in the absence of a definable precipitating event, such as a change in medication, diet or activity [20,21].

As 'glycaemic variability' has no universally agreed-upon definition, in our study patients were so classified if they had oscillations of blood glucose values from < 60 mg/dL

(3.3 mM/L) to > 250 mg/dL (13.9 mM/L) at least three times a week in an unpredictable and unexplained fashion, and if there was evidence that such a pattern had been present for at least 6 months previously [22,23]. The questionnaire used in our study was a modified version of the survey validated and applied in other studies of injection technique [2,24].

Our study inclusion criteria were having diabetes treated with insulin for at least a year, with the insulin being either self-administered or injected by a caregiver through either insulin pens or syringes. Patients excluded were those not using insulin and/or whose insulin treatment was only transient. The latter included women with gestational diabetes, decompensated patients with acute hyperglycaemia who did not ordinarily use insulin and hospitalized patients. Children under the age of 5 years, patients using insulin pumps and cases where there were protocol deviations were also excluded. Time since diabetes diagnosis was classified into the following five categories: 1 = 0–5 years; 2 = 6–15 years; 3 = 16–25 years; 4 = 26–30 years; and 5 ≥ 30 years. Time since initiating insulin was categorized as: 1 = 1–5 years; 2 = 6–13 years; 3 = 14–21 years; 4 = 22–29 years; and 5 ≥ 30 years.

The variables studied were: age; gender; type of diabetes; time since disease diagnosis; duration and type of insulin treatment; devices used; number of injections per day; total insulin doses per day; needle length used; frequency/extent of needle or syringe reuse; rotation of injection areas as described by the patient and site rotation as observed by the nurse; and presence, type and location of lipodystrophy. Correct site rotation was defined as changing the locations of the injection entry points by spacing them at least 1 cm apart to avoid repeated local tissue trauma.

In 78 patients with and without clinically detectable lipodystrophy, an ultrasound examination was made of the skin and SC tissue. A portable NanoMaxx® (SonoSite, Bothell, WA, USA) ultrasound unit was used, and a single ultrasound team performed all sonographic procedures. A specific LH 'echo signature' was identified, and used to diagnose and describe the lesions (Fig. S1; see supplementary material associated with this article online).

The study ran from 15 January to 30 September 2012. The study concept and objectives were explained to patients before obtaining their informed consent, and the study was conducted in compliance with the declaration of Helsinki and the European Union directive on good clinical practice.

Descriptive statistics were generated and contingency tables were evaluated using chi-square, and Pearson's and Fisher's exact tests; means were assessed by analysis of variance (ANOVA) and individually significant parameters by multivariate analysis. Data were analyzed using STATGRAPHICS Plus Version 5.1/SGWIN (Statistical Graphics Corp., Princeton, NJ, USA).

3. Results

A total of 474 subjects were initially included in the survey, but 44 of them failed to meet inclusion criteria or were excluded for one of the reasons stated above. Of the remaining 430 evaluable subjects, 230 (53%) came from PC and 200 (47%) from SpC; 177 (41%) had T1D and 253 (59%) had type 2 diabetes (T2D; Table 1). Also, 47 were children and 383 were adults. Of the 47 children, 35 were injecting themselves and 12 were receiving injections from their parents or caregivers. These latter children were all between 5 and 8 years of age.

The gender distribution was roughly half male and half female overall and in both diabetes subsets (Table 1). Their ages ranged from 5 to 76 years with a mean ± SD of 49 ± 23 years overall. The mean age of the T1D patients was 41 ± 23 years vs. 55 ± 21 years in the T2D.

In all, 78% of patients were using insulin analogues and 22% were taking human insulin. Of the T1D patients, 87.0% were being treated with a basal–bolus insulin regimen using rapid-acting analogues (Table 1). In the T2D group, treatment regimens were more heterogeneous: 40% were using slow-acting analogues alone; 28% were taking basal insulin plus a rapid-acting analogue; and 21% were using premixes. More than 90% of patients injected with insulin pens, while 294 (68%) of the patients used an 8-mm-long needle, 90 (21%) used a 5-mm one, 28 (7%) used a 12.7-mm needle and 17 (4%) used a 6-mm one. The median number of injections per day was three: four among the T1D cases; and two among the T2D, with 39% of the latter having only a single daily injection.

Although 287 (67%) of the patients claimed to rotate injection sites, the study nurse-observed an incorrect rotation technique in 145 (see definition of correct rotation above). In addition, 143 patients admitted to not rotating. Thus, 288 (67%) of the total patients either acknowledged not rotating or were rotating incorrectly.

Slightly less than two-thirds of patients (64.4%) had lipodystrophy, which was more commonly seen in T1D (76.3%) than in T2D (56.1%) patients. Overall, 1.4% had LA alone, and 0.9% had both LA and LH. Thus, as the overwhelming majority of cases of lipodystrophy were LH, the latter term will be used to refer to these lesions in the rest of this report. The abdomen was the most common LH-affected site, and it was also the most commonly used site of injection.

Patients with and without LH (Table 1) did not differ significantly by gender, proportion using pens, needle length preferences, frequency of insulin analogue use or use of antiseptic solutions to cleanse the skin before injecting. However, those with LH had higher daily doses of insulin, more injections per day and more basal–bolus therapy, and were more likely to reuse needles ($P < 0.05$ for all differences). They were also less likely to claim they rotated injection sites ($P < 0.05$) and much less likely to be observed to rotate correctly ($P < 0.001$). Rates of frequent unexplained hypoglycaemia and glucose variability were more than six to seven times higher in patients with LH than in those without ($P < 0.01$ for both).

More than half the patients said they reused needles at least once, with a higher rate of reuse among the T2D than T1D patients (Table 2). However, there were no significant differences between those who reused and those who did not in terms of the number of injections per day or quantity of insulin injected per day (mean 52 ± 26 IU in reusers vs. 49 ± 28 IU in those who did

Table 1
Data for patients according to diabetes (DM) type and presence of lipohypertrophy (LH).

	Total	T1D	T2D	LH present	LH absent
Patients (*n*)	430	177	253	277	153
Gender (M/F)	221/202	89/86	132/116	142/130	79/72
Age (years, mean ± SD)	49 ± 22.8	41 ± 23.2	55 ± 20.7	47 ± 23.8	54 ± 20.1
Since DM diagnosis (years, range)	6–15	6–15	6–15	6–15	6–15
(% in range)	(43.7)	(39.0)	(47.0)	(41.2)	(48.4)
Insulin treatment (years, range)	1–5	6–13	1–5	6–13	1–5
(% in range)	(44.2)	(37.3)	(54.9)	(35.0)	(64.1)
Primary care (*n*)	230	27	203	121	109
(%)	(53.5)	(15.3)	(80.2)	(43.7)	(71.2)
Speciality centre (*n*)	200	150	50	156	44
(%)	(46.5)	(84.7)	(19.8)	(56.3)	(28.8)
Pen use (%)	96.3	92.1	99.2	94.9	99.3
Needle length used (% using 8 mm)	68	56	77	69	67
Insulin dose (IU/day, mean ± SD)	51 ± 26.9	48 ± 20.7	53 ± 30.3	56 ± 26.9	41 ± 24.1
Injections/day (*n*, mean ± SD)	3.0 ± 1.5	4.2 ± 1.0	2.2 ± 1.2	3.4 ± 1.4	2.4 ± 1.5
(range)	(1–7)	(1–7)	(1–6)	(1–7)	(1–7)
Basal–bolus therapy (%)[a]	52.1	87.0	27.7	59.6	38.6
Basal therapy alone (%)[a]	24.0	1.1	39.9	15.5	39.2
Premixed therapy (%)[a]	14.2	4.5	20.9	15.2	12.4
Insulin analogue use (%)[b]	78.1	90.4	69.6	76.9	80.4
Reuse needles (at least once, *n*)	240	80	160	168	72
(%)	(56)	(45)	(63)	(61)	(47)
Rotation claimed (*n*)	287	125	162	145	142
(%)	(67)	(71)	(64)	(52)	(93)
Rotation correct (*n*)	106	35	71	6	100
(%)	(25)	(20)	(28)	(2)	(65)
Rotation claimed & correct (*n*)	100	34	66	5	95
(%)	(23)	(19)	(28)	(2)	(62)
Rotation correct & no reuse (*n*)	69	26	43	5	64
(%)	(16)	(15)	(17)	(2)	(42)
Presence of LH (*n*)	277	135	142	277	153
(%)	(64)	(76)	(56)	(100)	(0)
Skin cleansed with antiseptic (*n*)	69	27	42	50	19
(%)	(16)	(15)	(17)	(18)	(12)
Frequent unexplained HG (*n*)	117	71	46	108	9
(%)	(27)	(40)	(18)	(39)	(6)
Glycaemic variability (*n*)	146	89	57	136	10
(%)	(34)	(50)	(23)	(49)	(7)

T1D/T2D: type 1/type 2 diabetes; M/F: male/female; HG: hypoglycaemia.
[a] Percentages add up to < 100 because other therapies were used.
[b] Short- or long-acting analogues in a mixed or premixed preparation.

not). However, 86% of patients who reused needles either did not rotate injection sites or did so incorrectly.

There was a significant correlation between the presence of LH and the reuse of needles (Table 3, A), and a trend towards greater frequency of LH the more times the needle was reused (Table 4), which was greatest when the needle was reused more than five times. Of the patients in whom LH was found, 61% reported needle reuse. Of those who reused needles, 70% had LH (84% in T1D).

Out of all our 430 patients, 429 indicated whether they rotated sites or not and, in 386, the study nurses were able to verify by observation whether rotation was done correctly or not (Table 3, B–D). There was a strong association between the presence of LH and patient-reported rotation of injection sites (Table 3, B), with correct rotation of sites (as per nurse observation) having the strongest association (Table 3, C). Of the patients observed to rotate correctly (Table 3, D), only 5% had LH. Of patients with LH, 98% either did not rotate or rotated incorrectly (Table 3, C).

There were no significant differences in type of diabetes between patients who rotated injection areas (and did so correctly) vs. those not rotating (data not shown). However, patients who did not rotate or did so incorrectly injected more insulin per day (54 IU/day) than those who rotated correctly (44 IU/day; $P = 0.03$), whereas there were no differences in the number of injections per day between those who rotated and those who did not. Also, 67% of patients who correctly rotated injection areas claimed never to reuse needles vs. 40% of those who did not rotate correctly.

There was also a relationship between the presence of LH and the number of injections per day. If the patient had only one injection a day, as nearly 40% of our T2D cases did, then the prevalence of LH was low; as the number of injections per day rose, so did the prevalence of LH (data not shown).

Duration of insulin use correlated with LH prevalence: only 48% of those taking insulin for 1–5 years had LH vs. 71%, 87% and 91% of those using insulin for 6–13 years, 14–21 years and

Table 2
Data for diabetes patients according to injection site rotation and needle reuse.

	Total	Site rotation		Needle reuse	
		None or incorrect	Claimed & correct	Never reuse	Reuse at least once
Patients (*n*)	430	288	100	190	240
Gender (M/F)	221/202	141/142	56/43	102/87	119/115
Age (mean ± SD)	49 ± 22.8	47 ± 23.7	50 ± 21.5	47 ± 24.2	50 ± 21.6
Since DM diagnosis (years, range)	6–15	6–15	6–15	6–15	6–15
(% in range)	(43.7)	(44.1)	(48.0)	(46.8)	(41.3)
Insulin treatment (years, range)	1–5	6–13	1–5	1–5	1–5
(% in range)	(44.2)	(35.1)	(66.0)	(43.7)	(44.6)
Primary care (*n*)	230	125	63	83	147
(%)	(53.5)	(43.4)	(63.0)	(43.7)	(61.3)
Speciality centre (*n*)	200	163	37	107	93
(%)	(46.5)	(56.6)	(37.0)	(56.3)	(38.7)
Pen use (%)	96.3	95.1	99.0	92.6	99.6
Needle length used (% using 8 mm)	68	69	58	61	75
Insulin dose (IU/day, mean ± SD)	51 ± 26.9	54 ± 26.5	44 ± 24.9	49 ± 27.9	52 ± 26.0
Injections/day (*n*, mean ± SD)	3.0 ± 1.5	3.3 ± 1.4	2.6 ± 1.5	3.2 ± 1.6	2.9 ± 1.4
(range)	(1–7)	(1–7)	(1–6)	(1–7)	(1–6)
Basal–bolus therapy (%)[a]	52.1	57.6	45.0	54.7	50.0
Basal therapy alone (%)[a]	24.0	17.7	38.0	24.2	23.8
Premixed therapy (%)[a]	14.2	14.9	9.0	13.2	15.0
Insulin analogue use (%)[b]	78.1	77.1	87.0	80.5	76.3
Reuse needles (at least once, *n*)	240	172	33	190	240
(%)	(56)	(60)	(33)	(0)	(100)
Rotation claimed (*n*)	287	145	100	143	144
(%)	(67)	(50)	(100)	(75)	(60)
Rotation correct (*n*)	106	6	100	69	37
(%)	(25)	(2)	(100)	(36)	(15)
Rotation claimed & correct (*n*)	100	288	100	67	33
(%)	(23)	(0)	(100)	(35)	(14)
Rotation correct & no reuse (*n*)	69	2	67	69	37
(%)	(16)	(1)	(67)	(100)	(0)
Presence of lipohypertrophy (*n*)	277	264	5	109	168
(%)	(64)	(92)	(5)	(57)	(70)
Skin cleansed with antiseptic (*n*)	69	50	12	30	39
(%)	(16)	(17)	(12)	(16)	(16)
Frequent unexplained HG (*n*)	117	104	5	37	80
(%)	(27)	(36)	(5)	(19)	(33)
Glycaemic variability (*n*)	146	134	7	55	91
(%)	(34)	(47)	(7)	(29)	(38)

M/F: male/female; HG: hypoglycaemia.
[a] Percentages add up to < 100 because other therapies were used.
[b] Short- or long-acting analogues in a mixed or premixed preparation.

22–29 years, respectively. Patient's age did not emerge as a significant determinant of the presence of LH, although the type of diabetes did: 76% of T1D patients had LH vs. only 56% of the T2D ($P < 0.01$). The type of insulin used and specific regimen also had no influence on the development of LH (data not shown).

The mean insulin total daily dose (TDD) in our patients overall was 51 ± 27 IU and correlated with the presence of LH. Patients with LH averaged 56 IU/day while those without LH averaged 41 IU/day ($P < 0.001$). Significant differences in TDD proved to be attributable to the presence or not of LH when insulin dosages were analyzed in the two diabetes groups: 50 IU vs. 42 IU in T1D ($P = 0.03$) and 62 IU vs. 41 IU in T2D ($P = 0.01$), respectively.

To calculate the cost to both patients and the Spanish healthcare system of the additional insulin used by patients injecting into LH sites, data from the BD insulin injection profile were used to estimate the number of injectors in Spain among T1D and T2D patients. The result was an average additional 15 IU/day injected by patients with LH, with 21 IU/day used by the predominantly T2D patients. The mean cost per IU of insulin was estimated to be €0.02426 on averaging the cost of five 300-IU cartridges of the most commonly used insulin brands in Spain. This means that the total cost per year is more than €122 million, with the greatest proportion of 'incremental insulin consumption' attributable to T2D patients (Table S1; see supplementary material associated with this article online).

Table 3
Relationship between lipohypertrophy (LH) and needle reuse and injection site rotation.

	With LH (*n*)	Without LH (*n*)	Total
A. LH and reuse ($P = 0.0083$)			
Reuse	168	72	240
No reuse	109	81	190
Total	277	153	430
B. LH and patient-reported rotation ($P = 0.001$)			
Rotation	145	142	287
No rotation	131	11	142
Total	276	153	429
C. LH and nurse-observed rotation ($P = 0.0001$)			
Correct	6	100	106
Not correct	262	18	280
Total	268	118	386
D. LH and nurse-observed rotation + rotation claimed ($P = 0.0001$)			
Correct & claimed	5	95	100
Not correct or claimed	264	24	288
Total	269	119	388

Frequent unexplained hypoglycaemia was found in 117 (27.2%) of our patients and glycaemic variability in 146 (34.0%). Of those with LH, 39.1% had hypoglycaemia and 49.1% had glycaemic variability compared with only 5.9% and 6.5%, respectively, in those without LH (both $P < 0.01$; Table 1). Overall, 92% of patients with hypoglycaemia and 93% of patients with glycaemic variability had LH.

The following case of a study patient demonstrates the practical implications of our present findings. A 32-year-old man with an 18-year history of T1D was referred to the neurology department in May 2011 for severe nocturnal hypoglycaemia accompanied by clonic–tonic seizures since August 2010. Emergency services had been called to his home a number of times because of the seizures and they documented concomitant severe hypoglycaemia requiring glucagon injections. Brain magnetic resonance imaging (MRI) and electroencephalography (EEG) were both negative, and he was started on levetiracetam for seizure control. He was eventually referred to the diabetes unit in one of our study hospitals in August 2012 and, at that time, palpable LH was detected on both sides of his abdomen in his injection zones. He reported always injecting into the LH site. He was being treated at that time with basal–bolus therapy consisting of glargine and lispro at an insulin TDD of 136 IU. He used 12.7-mm needles and reused each one more than 10 times. His glycosylated haemoglobin (HbA_{1c}) was 6.9%. He was told to switch to 5-mm needles to avoid intramuscular (IM) injection, and to use each needle only once and then discard it. He was also instructed in the correct rotation technique for his injections and was strongly advised to not use LH areas. His insulin dose was reduced to avoid hypoglycaemia. He was seen again in December 2012 and reported having no seizures since August 2012. He had also not needed any emergency services and reported no nocturnal hypoglycaemia. At this time the levetiracetam was discontinued. On subsequently reporting two or three episodes of daytime hypoglycaemia per week, his insulin doses were further reduced, bringing his TDD of insulin to 48 IU, 86 IU less than 5 months previously. His HbA_{1c} remained 6.9%. Ultrasound images of his usual injecting sites and LH sites can be seen on Fig. S1 (see supplementary material associated with this article online), while his injection sites at the time he was first diagnosed with LH and the same sites at the time of his most recent visit in December 2012 are shown on Fig. S2 (see supplementary material associated with this article online). Striae can now be seen over these sites for reasons as yet unknown.

Table 4
Number of times needles reused in relation to presence of lipohypertrophy (LH).

Times needle used	LH (*n*)	No LH (*n*)	Ratio of LH/no LH[a]
1	109	81	**1.3**
2	38	33	**1.2**
3	37	12	*3.1*
4	20	9	*2.2*
5	18	7	*2.6*
6–10	55	10	5.5

[a] Subgroups are indicated by the bold, italic and normal fonts; there were no within-subgroup statistical differences, but between subgroup differences were $P < 0.05$.

4. Discussion

Ours is the first study to combine the patient's reporting with a nurse's observation of both injection sites and rotation practice. Our patient population is representative of diabetes patients in general, and our proportions of T1D and T2D patients and their relative ages are consistent with those previously published for questionnaire studies focused on injection technique [2,24].

The most robust finding of our study was the relationship between LH and the lack of proper rotation of injection sites. Of the patients who claimed to rotate sites and showed the

correct rotation technique, only 5% had LH. Of the patients with LH, 98% either did not rotate or rotated incorrectly. This reinforces the need to instruct patients not only on the importance of rotating sites, but also to provide an easy-to-remember method wherein each injection is made about a finger's breadth away (about 1 cm) from previous ones. Close examination of the skin for earlier puncture marks or the use of a grid system would also help patients to remember where previous injections had been given and so help them determine where the next one should go.

A correlation was observed between the presence of LH and the reuse of needles, with a trend towards more LH the more times the needle was reused (Tables 2 and 3). This was most notable when the needle was used more than five times (Table 4), a finding consistent with those found in two previous injection surveys [2,24]. It is also worth noting that, of the patients who did not reuse needles (each needle used only once), 109 still had LH while 81 did not, a ratio of 1:3 (Table 4). This ratio was similar to that also seen in those who used the needle twice (ratio 1:2) and may represent the underlying prevalence of such lesions with low-to-moderate reuse rates. However, there then appeared to be a stepwise increase in LH frequency from when needles were used once or twice (Table 4, ratio in boldface) to when they were used three to five times (Table 4, ratio in italics) and when they were used six or more times (Table 4, ratio in normal font). Nevertheless, the numbers in each of these groups varied considerably, so the hypothesis warrants further study.

There was also a strong relationship between the presence of LH and the number of injections per day, with a greater number associated with greater risk. Such a relationship has also been seen in earlier studies [6,12,24,25] and may be related to the increased trauma and increased exposure to insulin, itself a powerful growth factor.

LH was also associated with two of the most common and debilitating complications of insulin therapy: repeated unexplained hypoglycaemia and glucose variability. The rate of the former was more than six times higher in those with LH (39% vs. 6%), while glycaemic variability was seven times higher (49% vs. 7%). This strongly suggests that LH is a major contributor to these adverse clinical events. The corollary also supports this idea: 92% of our patients with hypoglycaemia and 93% of those with glycaemic variability had LH. It is also worth noting that LH is not always considered or looked for when patients present with these glucose aberrations, yet our present findings clearly suggest that it should be.

Another important finding of our study was the correlation between insulin TDD and the presence of LH and its cost to the healthcare system (Table S1; see supplementary material associated with this article online). Those with LH had significantly higher insulin TDDs both overall and by type of diabetes. T2D patients had the highest TDD differences and tend to be heavier in weight and have more insulin resistance compared with T1D patients, factors probably contributing to their greater insulin use. In our opinion, however, another major contributor was the habit of injecting into LH sites (Fig. S1, lower; see supplementary material associated with this article online), where the absorption properties of insulin are hampered [15,18]. It was also estimated that the cost of the additional insulin due to injecting into LH sites was more than €122 million for the Spanish healthcare system (Table S1; see supplementary material associated with this article online). This is clearly an opportunity for savings to be made by both patients and healthcare providers.

The aetiology of LH is probably multifactorial. Long-term exposure to insulin has been reported to be a key risk factor in a number of studies of LH [10,18]. Insulin's properties as a growth factor and similarity to insulin-like growth factor-1 (IGF-1) support this idea. Yet, other findings suggest it is not the only factor involved. Only some of the patients continuously exposed to insulin, such as those using insulin pumps, exhibit LH and not everyone who injects insulin has LH, as it arises mainly in those who repeatedly inject into the same site. If sites are carefully and systematically rotated, the incidence of LH should generally remain very low.

In the largest survey to date [24] of the injecting practices in 16 countries and involving 4352 patients, 47.9% of patients responded 'yes' to the question: 'Have you ever noticed swelling of fatty tissue or small bumps at your injection sites?' Adolescents and children had higher incidences of these lesions than adults. The abdomen and thigh were the sites with the majority of LH lesions, with buttocks having the least, but this may have only been a reflection of the frequency of injections at these respective body sites. After palpation, nurses found and measured 614 abdominal LH in a population of 4352 patients. The average diameter of the palpated lesion was 4.2 cm (SD 3.2), and size varied as a function of age, with the younger the patient, the smaller the mass.

However, it is important to not only diagnose LH, but also to give patients simple and practical advice on how to treat and/or prevent the condition. Using larger injection surface areas, rotating between and within these sites, and reusing needles less frequently are generally thought to be appropriate interventions even though they may not work in every case [26,27]. Patients should also be taught not to inject into LH sites, especially as a matter of habit and/or because it may be less painful [28]. Several studies have suggested that the best way to safeguard normal tissue is to properly and consistently rotate injection sites [29–31].

One strength of our study was the use of ultrasonography to detect and characterize LH. These lesions appear as homogeneous hyperechogenic densities filling part or all of the SC tissue at injection sites, and can clearly be distinguished from adjacent normal SC tissue (Fig. S1; see supplementary material associated with this article online). Also, using only one ultrasound team reduced interoperator variability. However, it was not possible to perform ultrasonography on all 430 of our patients, a limitation of our study. For this reason, it is not known how many LH lesions may have been detectable by ultrasound, but were missed clinically. A Russian study [31] in 50 T1D patients strongly supports the added diagnostic value of ultrasonography as they found that, while only eight of their 50 subjects had clinically evident LH, of the 42 who did not, an additional 33 showed ultrasound evidence of LH at injection sites. Only nine of the 50

had neither clinical nor echographic evidence of lesions. This high prevalence (82%) of LH was similar to our finding of a 76% prevalence of LH in our T1D subset of patients. Further future studies are warranted to confirm these findings.

Another future study would be to follow LH by ultrasound to determine the degree and timeline of its resolution subsequent to the use of an improved injection technique. This would allow an answer to the question often posed by patients with the condition: 'If I stop injecting into this site, how long will it take before it goes away?' A further related study could directly measure HbA_{1c}, glycaemic variability, hypoglycaemic events and changes in insulin dosages in patients who switch from injecting into LH to healthy tissue sites.

Another limitation of our study was the lack of information on chronic glycaemic control, or HbA_{1c} values. Such information would have provided a better understanding of the impact of LH on long-term glycaemic control and strengthen the analyses of potential cost savings to the healthcare system by taking measures to reduce LH.

Nevertheless, our study has helped to establish the relative risk of LH in terms of site rotation and needle reuse, and it is our intention to follow-up this analysis with the creation of a clinical scoring system that would inform management decisions based on where the patient falls on the scale. It is neither practical nor possible to examine every injection site on every patient at every visit, but such a scale would allow the triage of those at higher risk to more intensive monitoring. Also, a study similar to this one but focused exclusively on children would be useful.

Several important practical and public-health implications have emerged from our study. Correcting the two main risk factors for LH—incorrect site rotation and needle reuse—mostly involves better education of patients without large financial outlays. However, the clinical benefits would include lower rates of LH, fewer frequent and unexplained hypoglycaemia, and less glucose variability. In economic terms, the reduced use of insulin would lead to overall lower healthcare costs whereas, from an occupational standpoint, the reduction of LH implies a reduced workload for healthcare professionals as well.

Disclosure of interest

One author (K.S.) is employed by BD, a manufacturer of insulin syringes and pen needles. No company funding was given for this study. None of the other authors have any conflicts of interest.

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Appendix A. Supplementary materials

Supplementary materials (Figs. S1 and S2, and Table S1) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.diabet.2013.05.006.

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