ЛИПОГИПЕРТРОФИИ, ИНДУЦИРОВАННЫЕ ИНСУЛИНОМ: КЛИНИЧЕСКАЯ И УЛЬТРАЗВУКОВАЯ ХАРАКТЕРИСТИКА

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ОБОСНОВАНИЕ. Липогипертрофии – основное кожное осложнение инсулинотерапии. Данные о распространенности липогипертрофий у больных сахарным диабетом (СД) противоречивы, что может быть связано с недостаточной чувствительностью и субъективностью пальпации как метода диагностики данного осложнения. Надежность верификации липогипертрофий может быть повышена с помощью ультразвукового исследования (УЗИ).

ЦЕЛЬ. Сопоставить клинические и ультразвуковые характеристики и определить факторы риска индуцированных инсулином липогипертрофий у больных СД.

МАТЕРИАЛЫ И МЕТОДЫ. В исследование включено 82 пациента, в том числе 26 с СД 1 типа (СД1) и 56 с СД 2 типа (СД2). Длительность инсулинотерапии варьировала от 3 мес до 37 лет (медиана – 14 лет). Липогипертрофии выявляли с помощью пальпации и УЗИ. Протокол УЗИ включал серошкальную денситометрию, соноэластографию, исследование кровотока в режиме 3D-ангио. Выраженность ультразвуковых изменений оценивалась по балльной шкале. Техника инъекций инсулина оценивалась с помощью анкетирования. Уровень антител к инсулину в сыворотке крови определяли с помощью иммуноферментного анализа.

РЕЗУЛЬТАТЫ. При пальпации и ультрасонографии липогипертрофии выявлены у 57 и 80 (70% и 98%) больных. Площадь, эхоплотность и суммарный балл ультразвуковых изменений демонстрировали слабые положительные взаимосвязи с суточной дозой инсулина ($r=0,3$, $r=0,3$ и $r=0,35$ соответственно, все $p<0,006$). Суммарная площадь липогипертрофий в абдоминальной области оказалась достоверно меньше у больных, получавших аналоги инсулина, в сравнении с пациентами на человеческих инсулинах ($p=0,03$). Площадь липогипертрофий в абдоминальной области коррелировала с постпрандиальной гликемией ($r=0,35$, $p=0,001$). Наиболее частыми нарушениями техники инъекций инсулина оказались: редкая смена игл (70 человек, 85%), введение инсулина в участки липогипертрофий (47 человек, 53%). Уровень антител к инсулину не показал значимых корреляций с количеством и параметрами липогипертрофий.

ЗАКЛЮЧЕНИЕ. У больных СД1 и СД2 была выявлена высокая распространенность липогипертрофий в местах введения инсулина. Ультрасонография явилась более чувствительным методом диагностики липогипертрофий по сравнению с пальпацией. Наличие липогипертрофий у больных СД было ассоциировано с нарушениями техники инъекции инсулина и с более высокими суточными дозами инсулина.

КЛЮЧЕВЫЕ СЛОВА: сахарный диабет; инсулин; подкожная клетчатка; ультразвуковое исследование; антитела к инсулину

INSULIN-INDUCED LIPOHYPERTROPHY: CLINICAL AND ULTRASOUND CHARACTERISTICS

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BACKGROUND: Lipohypertrophy is primary dermal complication of insulin therapy. The data on the prevalence of lipohypertrophy in diabetic subjects are inconsistent, that may be due to the lack of sensitivity and subjectivity of palpation as diagnostic technique. Meanwhile, the reliability of lipohypertrophy detection can be increased by ultrasound.

AIMS: to compare clinical and ultrasound characteristics and to determine the risk factors of insulin-induced lipohypertrophy in diabetic subjects.

MATERIALS AND METHODS: We observed 82 patients, including 26 individuals with type 1 diabetes and 56 subjects with type 2 diabetes. Duration of insulin therapy varied from 3 months to 37 years (median 14 years). The sites of insulin injections were assessed by palpation and ultrasound. Visualization protocol included gray-scale densitometry, strain elastography, and 3D Doppler power ultrasound. Scaled evaluation of ultrasound sings was applied. Insulin injection technique was assessed by questionnaire. Serum levels of insulin antibodies were determined by ELISA.

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Received: 29.01.2018. Accepted: 10.05.2018.
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RESULTS: Lipohypertrophy was revealed by palpation and ultrasound in 57 and 80 patients (70% and 98%) respectively. Total lipohypertrophy area, acoustic density and total ultrasound score showed weak positive correlations with daily insulin dose (r=0.3, r=0.3 and r=0.35, respectively, all p<0.006). Patients receiving insulin analogues had smaller area of abdominal lipohypertrophy than those on human insulin (p=0.03). A positive correlation was found between abdominal lipohypertrophy area and mean postprandial glucose (r=0.35, p=0.001). A rare needle change and injections in lipohypertrophy sites were the most common deviations in insulin injection technique (70 and 47 subjects, 85% and 53% respectively). The levels of insulin antibodies showed no association with lipohypertrophy parameters.

CONCLUSIONS: Patients with type 1 and type 2 diabetes demonstrate high prevalence of lipohypertrophy in insulin injection sites. Ultrasonography is more sensitive method of diagnostics of lipohypertrophy compared with palpation. Insulin-induced lipohypertrophy is associated with errors in injection technique and higher insulin doses.

KEYWORDS: diabetes mellitus; insulin; subcutaneous tissue; ultrasonography; insulin antibodies

Development of lipodystrophy at injection sites is the principal cutaneous complication of insulin therapy. According to previous estimates, the incidence of insulin-induced lipodystrophy is 5%–53% [1-5]. The presence of lipodystrophy impairs the absorption of insulin from the administration site[6] and contributes to a deterioration in the quality of glycaemic control [4, 5, 7, 8].

Insulin lipodystrophy can manifest itself in two forms i.e. atrophic and hypertrophic. Improvement of the quality of insulin preparations and training of patients in injection techniques have significantly reduced the prevalence of atrophic lipodystrophy, but the prevalence of insulin-induced lipohypertrophy remains high [9]. Insulin-induced lipohypertrophy clinically manifests as tumour-like thickening of subcutaneous tissue (SCT), with the affected tissue often having a greater density than the surrounding tissue, or as multiple subcutaneous nodules at the injection sites. However, in some cases, lipohypertrophy is imperceptible on visual examination and palpation. It has been reported that the accuracy of lipohypertrophy diagnosis can be improved by using ultrasonography (US) [7, 8, 10]. However, currently there are no standard protocols for ultrasconographic evaluation of insulin administration sites in diabetic patients and the relationship between the type and severity of lipohypertrophy, assessed ultrasonographically, and the clinical course of diabetes mellitus (DM), has not been studied.

AIM

This study aimed to assess the relationship between the clinical features of diabetes and the ultrasonographic characteristics of subcutaneous lipodystrophic lesions, and to identify risk factors for insulin administration-induced lipohypertrophy in DM patients.

METHODS

Study design

We conducted a cross-sectional single-centre study. The study protocol included general clinical examination, palpation and ultrasonographic study of insulin injection sites, evaluation of insulin injection technique and measurement of the concentration of circulating anti-insulin antibodies.

Acceptance criteria

The study included patients with type 1 and type 2 diabetes mellitus (DM1 and DM2),who were >18 years of age, who had been self-administering insulin for the preceding three or more months, and who had provided written informed consent for their participation in this study. Patients administering any other drugs subcutaneously were excluded.

Research siteThe patients were enrolled in the clinic of the Scientific Research Institute of Clinical and Experimental Lymphology, a branch of the Federal Research Centre of the Institute of Cytology and Genetics, Siberian Branch of the Russian Academy of Sciences (Novosibirsk, Russia).

Study procedures

All the patients underwent a general clinical examination that included evaluation of their carbohydrate and lipid metabolism and screening for or monitoring of any chronic complications of DM.Lipohypertrophic sites were identified by visual and palpatory evaluation of insulin administration sites. Insulin injection technique was assessed using a questionnaire developed by us, which contained questions regarding the insulin therapy regimen, insulin type, site, depth and soreness due to injections, the frequency of change of injection sites, the length and frequency of needle change and insulin administration in induration sites.

The insulin injection sites were studied using US according to a unified protocol. The protocol aimed to measure the thickness of the SCT to determine the presence and size of lipohypotrophic lesions, and to assess their echogenicity, uniformity, acoustic solidity, rigidity and vascularity. The mean grey value (MG1) of lipohypertrophic sites and the density of regions of normal SCT (MG2) were determined, and the MG1:MG2 ratio was calculated. In compression sonoelastography mode, the rigidity indices of the lipohypertrophic sites (strain ratio: StR) were recorded and the values were compared with those for the normal SCT. A three-dimensional (3D) Doppler study of blood flow was also performed in 3D-angio mode, and indices of vascularisation of the lipohypertrophic sites were measured (vascularisation index, VI; flow index, FI and vascularisation flow index, VFI). These indices provide information regarding the blood supply to the region: VI indicates the number of vessels in tissue volume, FI indicates the intensity of blood flow (the number

of blood cells transported per unit time) and VFI is a combination of these two parameters. The severity of lesions was assessed on a point scale that describes the characteristics of the SCT and lipohypertrophic regions, using their acoustic properties and volumetric and densitometric measurements.

Fasting and postprandial glycaemia were assessed using measurements of capillary blood glucose at six points (three pointson an empty stomach and three points 2 h after a meal during a single day). The mean amplitude of glucose excursion (MAGE) and the low blood glucose index (LBGI) were calculated for the assessment of glycaemic variability (GV) [11].

The concentrations of anti-insulin antibodies in DM patients (70 patients) were compared with those of 10 healthy individuals (control group).

Primary study outcomes

The primary outcomes assessed in this study were the prevalence of insulin administration-induced lipohypertrophy in patients with DM1 or DM2 diagnosed using palpation and ultrasound, the size, acoustic solidity and vascularisation of lipohypertrophic sites, assessed ultrasonographically, the relationship between the presence of lipohypertrophy and the duration of insulin therapy, the daily dose of insulin, serum glycated haemoglobin (HbA1c) and GV and the relationship between the serum anti-insulin antibody concentration and the clinical and ultrasonographic characteristics of lipohypertrophic lesions.

Subgroup analysis

Given their clinical and demographic differences, data derived from patients with DM1 and DM2 were analysed separately.

Outcome measurements

Ultrasonographic studies were performed using a device featuring automatic 3D real-time scanning (Voluson E8 Expert BT-12; GE Healthcare, USA) and virtual convection scanning on a linear probe (11L-D Linear Array Probe, 4–10 MHz) for the study of superficial structures. The protocol included the use of Elastography Advanced 4D, OmniView+VCI, Volume Calculation II and software for the semi-automatic detection of the contours of structures and the calculation of their volume in the 3D reconstruction virtual organ computer aided analysis (VOCAL™) mode.

GV was calculated using blood glucose measurements made on 3 consecutive days using EasyGV (Version 9.0) [12].

Anti-insulin antibody concentration was determined in serum from fasting patients using an enzyme-based immunoassay (Orgentec Diagnostika GmbH, Germany). According to the manufacturer's instructions the normal concentration of antibodies'range from 0 to10 U/ml.

Ethical considerations

The study protocol was approved by the Ethics Committee of the Scientific Research Institute of Clinical and Experimental Lymphology (minute number 115, 24/12/2015).

Statistical analysis

Principles of calculating the sample size required

The required sample size was not calculated prior to the commencement of the study.

Methods of statistical data analysis

Statistical analysis was performed using STATISTICA 10 (StatSoft, Inc, 2011, USA). The data obtained were assessed for normality using the Kolmogorov-Smirnov and Shapiro–Wilk tests. Given that the distribution of most of the characteristics studied was not normal, non-parametric methods of statistical analysis were applied. Intergroup differences were assessed using the Mann–Whitney test or the Kruskal–Wallis test. Relationships between the characteristics were assessed using Spearman correlation analysis. The significance level was set at $P < 0.05$. Data are presented as medians, 25th and 75th percentiles, and minimum and maximum values.

RESULTS

Study participants

The study included 82 patients, 27 men and 55 women, aged 19–years (median age, 60.5 years). The duration of DM varied from 3 months to 46 years (median, 16 years) and body mass index (BMI) was 19.1–46.3 kg/m2 (median, 30.7 kg/m2). Serum HbA1c was 6.4%–15.6% (median, 8.7%). Twenty-six of the participants had DM1, and 56 had DM2. The clinical characteristics of the patients with DM1 or DM2 are presented in Table 1.

All DM1 patients administered the basal-bolus insulin therapy(21 patients were administering multiple daily injections and five were administering continuous subcutaneous infusion). Among those using pumps, two patients were transferred to insulin infusion in the departmentand the other three were administering continuous subcutaneous infusions for 1, 7 and 9 years (previously all of these patients were administering insulin as multiple injections for 10–20 years). One patient administered short-acting human insulin therapy, while the remaining 25 patients administered rapid-acting analogues of human insulin (insulin lispro, aspart or glulisin). Long-acting human insulin analogues were also being administered by all patients who received multiple injection insulin (glargine 100 U/ml or detemir).

Among the DM2 patients, 14 were administering basal insulin alone (1–2 injections of a long-acting insulin analogue daily), six were administering combined insulins (five were administering a mixture of human insulins and one was administering a mixture of human insulin analogues). The remaining 36 patients were treated with basal-bolus insulin therapy. 15 of them were administering short-acting human insulin, 21 a rapid-acting human insulin analogue (lispro or aspart), 13 neutral protamine hagedorn-insulin and 23 a long-acting human insulin analogue (glargine 100 U/ml or detemir). In addition to insulin, 34 DM2 patients were taking metformin, 8 were taking sulphonylureas and three were taking glucose and sodium cotransporter inhibitors.

The completed questionnaires showed that 47 (53%) patients used only abdominal SCT for insulin injection,

Table 1. Clinical characteristics of participants with type 1 or type 2 diabetes

Character	DM1 (n=26)		DM2 (n=56)	
	Median (25th; 75th percentile)	Min–Max	Median (25th; 75th percentile)	Min–Max
Age, years	32 (29; 54)	19-67	62 (57.5; 67.5)	23-83
BMI, kg/m2	24.8 (21; 30.7)	19.1-37.3	33.7 (27.3; 38.9)	20.5-46.3
DM duration, years	14 (10; 23)	0.3-46	16 (11; 22)	1-38
Duration of insulin therapy, years	14 (10; 23)	0.3-46	6 (3; 10)	0.3-37
Daily dose of insulin, U	49 (40.5; 68)	23-88	48 (34; 76)	8-110
Daily dose of insulin, U/kg	0.7 (0.6; 0.9)	0.4-0.9	0.6 (0.4; 0.8)	0.1-1.5
HbA1c, %	9.1 (7.7; 9.6)	6.6-11.5	8.6 (7.7; 10.4)	6.4-15.6
MAGE, mmol/L	4.75 (3.7; 5.9)	1.75-10.1	4.1 (3.2; 5.1)	1.8-12.5
LBGI, RU	1.18 (0.1; 3.2)	0-17.8	0.02 (0; 0.7)	0-7
Total cholesterol, mmol/L	5.0 (4.1; 5.7)	3.5-8.3	5.4 (4.8; 6.1)	3.3-8.0
LDL cholesterol, mmol/L	3.4 (2.5; 3.8)	0.7-5.7	3.3 (2.8; 4.1)	1.2-5.0
HDL cholesterol, mmol/L	1.6 (1.3; 1.7)	0.9-3.5	1.2 (1.0; 1.4)	0.7-1.9
Triglycerides, mmol/L	0.9 (0.7; 1.2)	0.4-8.0	1.8 (1.3; 2.6)	0.7-7.5
Estimated GFR, ml/min/1.73 m2	80 (72; 88)	58-107	66 (52; 83)	30-115

Notes: LDL – low-density lipoprotein; HDL – high-density lipoprotein; GFR – glomerular filtration rate (according to CKD-EPI, 2009).

while 30 patients (37%) used abdominal and thigh SCT, two patients used the shoulder area, another two used the shoulder area and abdominal SCT, and one used the buttocks.

Primary study results

Visual inspection and palpation of the sites of insulin administration identified lipohypertrophy in 57 (70%) patients. Most frequently, 1–2 sites of induration were recorded (in 50 patients [88%] lipohypertrophy was identified by palpation), but seven (12%) patients had 3–6 sites of lipohypertrophy. Lipohypertrophy was most frequently identified in the anterior abdominal wall and was less frequently identified on the lateral surface of the thighs, shoulders and buttocks.

Lipohypertrophy was detected in 80 (98%) patients, including 25 DM1 patients and 55 DM2 patients on USs of the injection sites. The total area of lipohypertrophy on the anterior abdominal wall varied from 50 to 1,847 mm2 (median, 370 mm2). In most cases (91.5%), the lipohypertrophic areas were characterised by higher echogenicity of the relatively unaltered SCT (Figure 1). The median values of MG1 and MG2 were 37.8 and 29, respectively ($p < 0.001$). Compression sonoelastography showed that there was a heterogeneous increase in rigidity in hypertrophic areas compared to unaffected areas (Figure 2). 3D-angiography revealed hypovascular zones surrounding sites of lipohypertrophy (Figure 3), which was confirmed by quantitative assessment of blood flow parameters (Fig. 4).

The ultrasonographic characteristics of lipohypertrophic sites in patients with DM1 or DM2 are presented in Table 2. This shows that for the majority of parameters there were no significant differences between DM1 and DM2 patients.

Correlation analysis revealed a statistically significant relationship between the total area of lipohypertrophy and the thickness of the SCT of the anterior abdominal wall ($r = 0.55$, $p < 0.0001$), BMI ($r = 0.3$, $p = 0.003$) and waist circumference ($r = 0.42$, $p = 0.0001$). There was an association between the area of lipohypertrophy and SCT thickness for both DM1 and DM2 patients ($r = 0.68$, $p = 0.0001$ and $r = 0.53$, $p = 0.005$, respectively). However, significant associations with BMI and waist circumference were identified only in DM2 patients ($r = 0.3$, $p = 0.02$ and $r = 0.32$, $p = 0.02$, respectively). Parameters characterising the blood supply in the lipohypertrophic areas were expected to correlate with each other (VFI closely correlated with VI ($r = 0.9$, $p < 0.0001$) and FI ($r = 0.47$, $p < 0.0001$)), but these did not correlate with acoustic solidity (MG1 and MG1:MG2 ratio) or the rigidity coefficient StR. The lipohypertrophic area, acoustic solidity (MG1:MG2 ratio), overall ultrasonographic lipohypertrophy index and anterior abdominal wall SCT thickness all showed weak positive correlations with daily insulin doses ($r = 0.3$, $p = 0.006$; $r = 0.3$, $p = 0.006$; $r = 0.35$, $p = 0.001$ and $r = 0.24$, $p = 0.03$, respectively). The associations between the daily doses of insulin and the area of lipohypertrophy or the anterior abdominal wall SCT thickness were closer for DM1patients ($r = 0.47$, $p = 0.02$ and $r = 0.57$, $p = 0.002$, respectively). However, there were no significant correlations among the number of insulin injections per day, the duration of insulin therapy and the ultrasound parameters studied.

Effects on the SCT in the areas of insulin injection were identified using US, even following only a short duration of insulin therapy. In particular, lipohypertrophy was detected in five patients who had been administering insulin for 3–12 months. As an example, we relate the details of a specific case below.

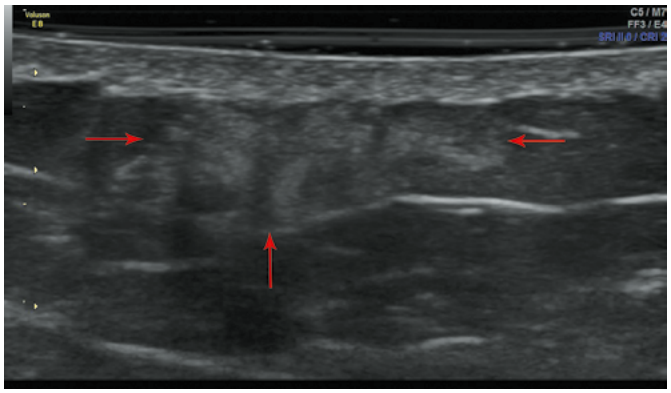

Fig. 1. Hyperechogenic areas (arrows) in the subcutaneous tissue of the anterior abdominal wall, consistent with lipohypertrophy, in the zone where insulin was being injected by a diabetes mellitus patient. Mean grey scanning in B-mode.

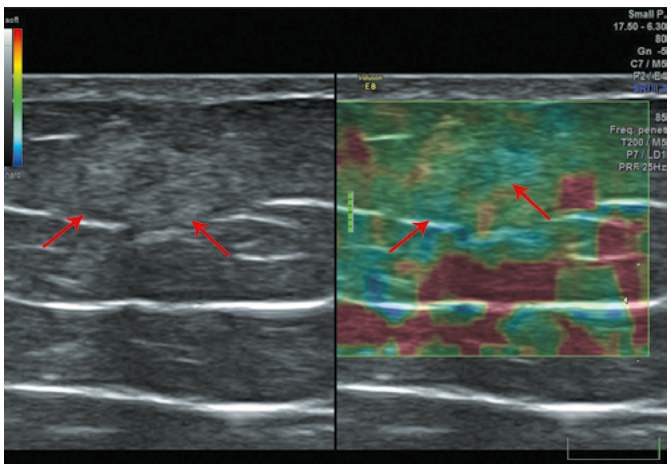

Fig. 2. Heterogeneous site of greater rigidity (arrows) of the subcutaneous tissue of the anterior abdominal wall, consistent with lipohypertrophy, in a diabetes mellitus patient. Left: mean grey scanning in B-mode; right: real-time compression sonoelastography. Areas of greater rigidity appear blue.

Patient P, 22 years old, had been diagnosed with DM 3 months previously, when basal-bolus insulin therapy was prescribed. The patient had been injecting human insulin (Rosinsulin R and C), 100 U/ml insulin glargine (Lantus) and insulin lispro (Humalog) for the preceding month. The daily dose of insulin had been 22–26 U (0.46–0.54 U/kg) and the HbA1c concentration was 7.6%. Insulin had been injected into the anterior abdominal wall and the SCT over the lateral hip area. Visual examination and palpation of the injection sites over the hip area identified areas of SCT induration of up to 1 cm in size. Ultrasonographic examination of the injection sites identified areas of greater echogenicity in the right and left SCT overlying the hip of up to 16 mm2. The values for the echogenicity indices in the mean grey densitometry mode on the right side were MG1 52.2, MG2 39 and MG1 52.7, with MG2 39 on the left side. The rigidity coefficient StR was 1.0 on the right and 1.64 on the left. The overall ultrasonographic index was 8 on the right and 9 on the left.

The total area of lipohypertrophy in the abdominal region was significantly lower in patients administering insulin analogues than in those administering human insulins (median 200, range 139–385.5; and mean 406.5, range 208–603.5 mm2, respectively; p = 0.03), despite the absence of significant differences in BMI, insulin dose, duration of insulin therapy or the number of injections between these groups.

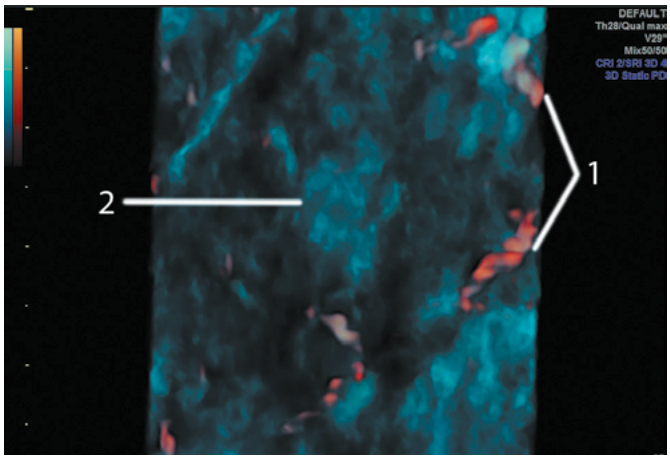

Fig. 3. Reconstruction of a lipohypertrophic site in the subcutaneous tissue of the anterior abdominal wall, in the zone where insulin was being injected, in a diabetes mellitus patient. 3D-angio mode. 1. Blood vessels in the subcutaneous tissue (Power Doppler mode). 2. Hypovascular zone at the site of lipohypertrophy.

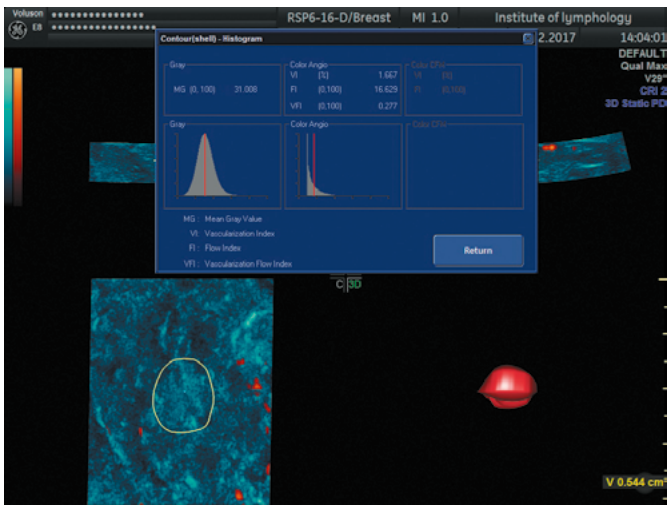

Fig. 4. Analysis of the vascularisation of a site of lipohypertrophy in the subcutaneous tissue of the anterior abdominal wall, in the zone where insulin was being injected by a diabetes mellitus patient, using VOCAL (Virtual Organ Computer Aided anaLysis) software. Above: vascularisation indices; bottom left: reconstruction of the lipohypertrophy site in 3D-angio mode; bottom right: a 3D reconstruction of the lipohypertrophic site.

The presence of lipohypertrophy was identified in five DM1 patients who were administering analogues of insulin using a pump. In two patients, lipohypertrophy had developed previously, when multiple insulin injections were being administered, but in three patients it had developed during the period of infusion. The area of lipohypertrophy in these three patients ranged from 77 to 252 cm2.

The area of lipohypertrophy in the abdominal region positively correlated with postprandial glycaemia (r = 0.35, p = 0.001). In DM2 patients, the area of lipohypertrophy correlated with serum triglyceride concentration (r = 0.35, p = 0.008). The FI blood flow index showed a weak negative correlation with the level of postprandial glycaemia (r = –0.29, p = 0.01). The overall ultrasonographic lipohypertrophy index correlated positively with serum triglycerides (r = 0.41, p = 0.0001) and uric acid (r = 0.38, p = 0.0004) and negatively with HDL cholesterol (r = –0.4, p = 0.0002). The same parameters correlated with the anterior abdominal wall SCT thickness (triglycerides: r = 0.52, p < 0.0001; uric acid: r = 0.49; p < 0.0001 and HDL cholesterol: r =

Table 2. Ultrasonographic characteristics of lipohypertrophic sites in the anterior abdominal wall of patients with DM1 or DM2

Parameter	DM1 (n=26)	DM2 (n=56)	P-value
Subcutaneous tissue thickness, mm	13 (11; 18)	23.8 (18; 28.5)	0.0001
Total area of lipohypertrophic sites, mm2	382 (212; 539)	370 (202; 540)	0.22
MG1	37.6 (33.0; 47.7)	37.9 (33.5; 44.1)	0.91
MG2	29.4 (26.4; 31.0)	29.4 (27.9; 31.6)	0.69
MG1/MG2	1.33 (1.10; 1.59)	1.24 (1.10; 1.43)	0.42
StR	1.49 (0.93; 2.1)	1.41 (0.9; 1.9)	0.31
VI	0.70 (0.35; 3.9)	0.67 (0.21; 1.15)	0.86
FI	19.5 (16.4; 22.3)	19.0 (16.0; 21.3)	0.86
VFI	0.12 (0.06; 0.36)	0.12 (0.03; 0.46)	0.88
Ultrasonographic lipohypertrophy index	7.8 (6.0; 10.3)	11 (10; 13)	0.0004

−0.38, p = 0.0004). There were no significant correlations among the ultrasonographic indices of lipohypertrophy, concentration of HbA1c and GV indices.

The most frequent errors in insulin injection technique revealed during the survey were infrequent changing of needles or infusion sets (70 patients, 85%), insulin administration in locations with pre-existing lipohypertrophy (47 patients, 53%), and errors in the storage and use of insulin (34 patients, 41%). Forty-three patients (52%) noted greater soreness at the site of injections when insulin was injected into sites of induration.

The concentration of anti-insulin antibodies in DM1 patients ranged from 0 to 85.2 U/ml (median, 3.5 U/ml) and an antibody concentration >10 U/ml was measured in six patients (23%). Among DM2 patients, the concentration of antibodies to insulin ranged from 0 to 24.4 U/ml (median, 2.9 U/ml), with eight patients having an antibody concentration >10 U/ml (17%). In all the patients included in the control group the antibody concentration was within the normal range (0–4.6 U/ml; median, 2.3 U/ml). The anti-insulin antibody concentration did not correlate with either the number of lipohypertrophic sites or their ultrasonographic parameters.

Adverse events

During the study no adverse events were recorded.

DISCUSSION

In DM1 and DM2 patients, a high prevalence of lipohypertrophy was found at the sites of insulin administration. US was a more sensitive method of diagnosing lipohypertrophy than palpation. The protocol for ultrasonographic evaluation of the insulin injection sites, including grey scale densitometry, sonoelastography and 3D Doppler examination of blood flow, using quantitative evaluation of each parameter, provides a detailed characterisation of insulin administration-induced lipohypertrophy. The presence of lipohypertrophy in DM patients was also associated with errors in the technique of insulin administration and with higher daily doses of insulin.

Lipohypertrophy is one of the most frequent modern complications of insulin therapy. Data regarding the prevalence of lipohypertrophy among DM patients administering insulin differ significantly among the published studies, primarily due to variation in the technique used to identify this complication. In most previous studies, the prevalence of lipohypertrophy was assessed only by palpation. A meta-analysis of 26 studies, including a total of 12,493 DM patients, showed that the prevalence of lipohypertrophy identified by palpation is 38%. It is interesting that among DM2 patients, the prevalence was found to be higher than among DM1 patients (49% and 34%, respectively) [13]. However, visual assessment and palpation of insulin injection sites are associated with a high degree of subjectivity. It has been shown that training of medical personnel in the technique of injection site palpation significantly improves the frequency of identification of lipohypertrophy in DM patients [14]. In our study, using a targeted visual assessment and palpation of injection sites, lipohypertrophy was detected in 70% of patients. However, it was detected in 98% of the patients when sonoelastography was added to the diagnostic protocol. Previously, Volkova et al. reported that lipohypertrophy at the sites of insulin injection is detected much more frequently using US than using palpation (in 87% and 31% of DM patients, respectively) [15]. The data obtained in this study are consistent with the notion that there is significant under-diagnosis of insulin administration-induced lipohypertrophy in clinical practice [9].

The main reason for the development of lipohypertrophy is the anabolic effect of insulin on the synthesis of fat and protein which explains the fact that lipohypertrophy develops even in patients administering genetically engineered insulin preparations or continuous subcutaneous insulin infusions by pump [16]. The generation of anti-insulin antibodiesis also considered to be involved in the effects of insulin injection in the SCT [9]. However, our study did not reveal any correlation between the ultrasonographic characteristics of lipohypertrophic areas and the concentration of circulating anti-insulin antibodies. Therefore, it is likely that immune reactions do not play a significant role in the development of lipodystrophy.

The importance of various characteristics (chemical structure, concentration, type and concentration of stabilisers, and effect prolongators) of insulin preparations and insulin therapy (duration and daily doses) as risk factors for lipohypertrophy remains unclear. In our study, preliminary data were obtained on a smaller scale regarding lipohypertrophy in DMpatients administering insulin analogues than from patients who were administering human insulins. It can be assumed that insulins with a smaller volume of distribution in the SCT have advantages in terms of the risk of lipohypertrophy, but this issue requires further research. In our study, any relation between the ultrasonographic characteristics of lipohypertrophy and the mode or duration of insulin therapy was not observed; however, it was observed that lipohypertrophy can develop during the first year of treatment with insulin.

Errors in the technique of insulin injection may also predispose to the development of lipohypertrophy. Analysis of insulin injection technique in DM1 and DM2 patients, conducted in 16 countries around the world, revealed a number of typical errors, including insulin administration in the same area during a day (21%) and continual or episodic insulin injection into lipohypertrophic sites (3% and 26%, respectively) [2]. When the situation in Russia was analysed, it was found that 43.5% of patients injected into the same anatomical area, 41.5% had induration at the injection sites and more than half of these patients continued to inject into the affected areas [1]. Our data also demonstrated frequent errors in insulin administrationby DM patients with the administration of insulin into lipohypertrophic sites being one of the most common mistakes. Thus, compliance with recommendations regarding the technique of injection or infusion of insulin [17] is the most important for the prevention of lipohypertrophy.

We identified correlations between the area, acoustic solidity, and the overall ultrasonographic lipohypertrophy score and the daily dose of insulin. Other authors have also shown associations between the presence of lipohypertrophy and higher doses of insulin [5], which may be explained by impaired insulin absorption from areas of altered SCT. This was illustrated by the administration of insulin lispro into an area of lipohypertrophy being associated with a lower area under the curve of insulin concentration in the blood during the first 5 h after the injection. In this example, the peak postprandial plasma glucose concentration occurs at mean 15 min later and is 25% higher than that when insulin is injected into a normal area SCT [6, 18]. These data are consistent with the positive correlation we identified between the area of lipohypertrophy in the abdominal region and postprandial glycaemia, and with the negative correlation between the blood flow index in the area of lipohypertrophy and postprandial glycaemia. Thus, an alteration in insulin kinetics when it is administered into a lipohypertrophic site may contribute to excessive fluctuations in postprandial glucose concentrations.

In our study, we also demonstrated associations between the overall ultrasonographic lipohypertrophy index and the serum concentrations of triglycerides, uric acid and HDL cholesterol. However, these associations are not direct, instead being mediated through differences in the accumulation of fat in the abdominal SCT and/or hyperinsulinaemia. We showed positive correlations between the total area of lipohypertrophy in the abdominal SCT, the SCT thickness in the anterior abdominal wall, BMI and waist circumference, and the daily dose of insulin. In addition, correlations were identified between the SCT thickness in the anterior abdominal wall; the serum concentrations of triglycerides, HDL cholesterol and uric acid; and the daily dose of insulin. Thus, the mechanisms underpinning the associations between lipohypertrophy and metabolic parameters require further study.

One of the limitations of this study is its cross-sectional design that does not permit the identification of cause-effect relationships between variables. Because the study was conducted at one clinical centre, it included only hospitalised patients and had a relatively small sample size, there is a possibility of systematic bias in the assessment of the prevalence of lipohypertrophy among DM patients. In addition, the heterogeneity of the stu+lin therapy, and the type and dose of insulin, could also conceal some of the relationships between the studied variables.

CONCLUSION

Insulin-induced lipohypertrophy remains a significant problem in diabetology. To our knowledge, this study is the first in which quantitative ultrasonographic parameters associated with insulin administration-induced lipohypertrophy have been studied using a comprehensive protocol, including mean grey densitometry, sonoelastography and a 3D Doppler examination of blood flow. This protocol enables the provision of a detailed sonographic description of insulin administration-induced lipohypertrophy.

The study demonstrated a high prevalence of hypertrophic processes in the SCT where insulin had been injected by DM1 and DM2 patients, the possibility of early hypertrophy (with a duration of insulin therapy of <1 year), and connections with poor injection technique, daily insulin dose and postprandial glycaemia.

It is clear that the visual examination and palpation of injection sites should be an obligatory part of the assessment of patients However, to identify areas of lipohypertrophy that are not detectable during these assessments, especially in patients with unexplained fluctuations in glycaemia, it is advisable to evaluate injection sites ultrasonographically. In patients with fairly generalised lipohypertrophy, US can be useful for the selection of areas of normal SCT for subsequent injections of insulin. In addition, the discussion of insulin injection technique with patients should remain among the priorities of training programmes and for the monitoring of DM patients administering insulin.

ADDITIONAL INFORMATION

Source of financing. The work was performed at the expense of the state task of the Scientific Research Institute of Clinical and

Experimental Lymphology, a branch of the Federal Research Centre of the Institute of Cytology and Genetics of the Siberian Branch of the Russian Academy of Sciences.

Conflict of interest. The authors declare no obvious and potential conflicts of interest related to the publication of this article.

Author contributions. V.V. Klimontov – the concept and design of the study, data analysis, writing the text; M.M. Lazarev – ultrasonography, analysis and statistical data processing; A.A. Makhotin – development of the protocol of ultrasound for insulin injection sites, data analysis; L.A. Anisimova – ultrasonography; A.Yu. Letyagin – the concept and design of the study, data analysis; D.M. Bulumbaeva, E.A. Koroleva – collection of general clinical data, analysis of results; A.P. Lykov – study of antibodies to insulin.

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ЦИТИРОВАТЬ:

Климонтов В.В., Лазарев М.М., Махотин А.А., Летягин А.Ю., Анисимова Л.А., Булумбаева Д.М., Королева Е.А., Лыков А.П. Липогипертрофии, индуцированные инсулином: клиническая и ультразвуковая характеристика // *Сахарный диабет*. — 2018. — Т. 21. — №4. — С. 255-263. doi: 10.14341/DM9549

TO CITE THIS ARTICLE:

Klimontov VV, Lazarev MM, Makhotin AA, Letyagin AY, Anisimova LA, Bulumbaeva DM, Koroleva EA, Lykov AP Insulin-induced lipohypertrophy: clinical and ultrasound characteristics. *Diabetes Mellitus*. 2018;21(4):255-263. doi: 10.14341/DM9549