Lipedema patients show a distinctly altered Quantitative Sensory Testing (QST) profile

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Abstract

Lipohyperplasia dolorosa (LiDo), also known as lipedema, is a painful subcutaneous adipose tissue disorder. While the characteristic bilateral accumulation of adipocytes in extremities sparing hands and feet is investigated, an objective characterization of pain and the sensory system of LiDo patients is missing. Accordingly, progress to overcome the unsatisfying response to pain-therapeutics of patients of this widespread, lifelong, and severe disease is missing.

We characterized the sensory detection profile of painful and non-painful stimuli in 20 non-obese LiDo patients and 20 waist-to-height-ratio matched controls using the clinically approved QST-protocol of the German Research Association on Neuropathic Pain (DFNS e.V.). Further, pain-reports and participants'-psychometry was assessed using the German Pain Questionnaire.

LiDo patients showed no overt psychometric abnormalities. LiDo pain appeared as somatic rather than neuropathic or psychosomatic aversive. All QST measurements were normal with the selective exception of two: The pressure pain threshold (PPT) was strongly reduced and the vibration detection threshold (VDT) was strongly increased selectively at the affected thigh. In contrast, sensory profiles at the dorsum of the hand were normal. ROC-analysis of the combination of PPT and VDT of thigh versus hand shows high sensitivity and specificity, categorizing correctly 96.5% of the measured participants as LiDo patients or healthy controls, respectively.

Thus, we propose to assess both, PPT and VDT, at the painful thigh and the pain-free hand as basis to develop a combined PVTH-score for differential diagnosis as a fast and convenient bedside test for the identification of non-obese LiDo patients.

Introduction

Lipohyperplasia dolorosa (LiDo), also known as lipedema, is a disease of the subcutaneous adipose tissue [2; 12]. It is characterized by subcutaneous bilateral deposition of adipose tissue in limbs and arms not affecting feet or hands [1; 10; 15; 19; 28; 36; 41; 42; 46; 48]. Depositions are unresponsive to dietary restrictions or physical activity [19; 36; 47]. LiDo affects almost exclusively women and typically manifests concomitant with hormonal changes, such as puberty, pregnancy, or childbirth [3; 16]. The etiology and the spectrum of physiological changes are only starting to emerge.

Pain is a major characteristic of LiDo [8; 11; 21; 25; 40; 42]. It is perceived in the affected extremities and differentiates LiDo from non-painful phenotypes such as obesity or lymphedema [8]. The etiology of LiDo pain is currently unknown and patients are mostly unresponsive to analgesics. This lasting pain thereby greatly aggravates the burden of the disease [21; 40].

Acknowledging the defining role of pain for LiDo, a staging system according to painfulness has been proposed [40]. Staging ranged from stress-induced spontaneous pain to permanent pressure pain accompanied by persistent long-lasting pain attacks. This system has not been embraced by the community, potentially due to low compatibility with clinical pain categories such as nociceptive, inflammatory, neuropathic, or psychosomatic pain. In addition, such grading does not yet allow access to etiology or therapeutic approaches. Accordingly, what kind of pain is prevalent in LiDo patients and if there are also other sensory aberrations has not been clearly defined.

Assessment of pain is difficult in general as it contains physiological-sensory and psychological components [35]. Accordingly, pain assessment depends mostly on subjective self-reports of patients often recorded by pain questionnaires such as “Deutsche Schmerzfragebogen” or “painDETECT” [10; 20; 30]. Only recently, one study attempted to more objectively characterize LiDo pain by combining a questionnaire-based test with physical testing of one sensory modality with in part inconclusive results [11]. Whether measurements of a broader range of sensory

modalities may capture sensory alterations specific to LiDo patients, has not been attempted so far.

Accordingly, we now aimed to characterize the somatosensory phenotype in LiDo-patients more broadly using the clinically approved standardized approach of quantitative sensory testing (QST) as developed by the German Research Association on Neuropathic Pain (DFNS) [29; 34; 37; 38]. Conducting 7 tests, 13 different sensory thresholds are determined, which allows access to pathological mechanisms of e.g. specific sensory fiber types. A high level of objectivity was assured by controlling the technical proficiency of the measuring personal as well as reducing patient subjectivity by averaging over repetitive tests. Measuring the unaffected hands in addition to the affected thigh served as patient-specific internal control. Finally yet importantly, we focused on non-obese patients, avoiding the unsolved problem how to differentiate LiDo from obesity. The study was accompanied by a comprehensive standard pain questionnaire used in Germany to investigate patients' psychometry and pain descriptions to provide a comprehensive analysis of the hallmarks of LiDo pain. The potential of the results was tested, if they could serve as basis to develop a diagnostic test for identification of LiDo patients.

Materials and Methods

Patients

This project was conducted in accordance with the declaration of Helsinki and the ICH E6 Good Clinical Practice (GCP) guidelines. The study was fully approved by the ethical committees of the medical faculty of the University of Cologne (20-1594) and of the Ärztekammer Nordrhein (2021239). The trial was registered at the German Clinical Trials Register (DRKS00030509). All participants provided signed informed consent prior to their inclusion.

In total, 20 patients with LiDo and 20 healthy control participants were recruited according to the inclusion criteria. All participants were female, between 18 and 40 years, and had a body mass index (BMI) below 30 kg/m². Participants of the LiDo group were recruited via the CG Lympha clinic for surgical lymphology in Cologne. They presented with a clinical tentative diagnosis of LiDo according to ICD-10 criteria and the diagnosis was confirmed by a trained physician of the CG Lympha team. Healthy participants for the control group were addressed via flyer and email within the University Hospital Cologne and the University of Cologne.

General exclusion criteria were diseases that influence the sensory system, such as Parkinson's disease, multiple sclerosis, polyneuropathy, amongst others. In addition, patients were excluded if topical analgesics were used or if alterations in sensory perception or an official pain diagnosis was known.

Quantitative Sensory Testing

Quantitative sensory testing (QST) was performed according to the protocol of the German Research Association on Neuropathic Pain (DFNS) [29; 34; 37; 38]. Communication occurred in German. Testing was performed by the same DFNS-trained experimenter preferably in the morning hours, from November 2021 through October 2022. All measurements were conducted in quiet plain rooms without any disturbances. In brief: All individuals were measured at the lateral thigh as one of the areas with the greatest sensation of pain in LiDo patients and the dorsum of the hand as an intraindividual unaffected control area. Before the measurement, each test was

demonstrated at an independent area and all participants were familiarized with the instructions. Participants were encouraged to ask questions immediately when they arose. Then the procedure was clarified without providing further information than the script allowed. Seven different tests were conducted to assess 13 different parameters in a standardized manner using the official test instructions provided by the DFNS. Thermal thresholds were determined using the Thermal Sensory Analyser II (TSA-II) with a thermode of 9 cm² contact area (Medoc Ltd., Israel) and the corresponding Software Medoc Main Station Version Arbel 6.4.0.22 licensed for TSA-II and AlgoMed on a standard windows notebook. Stimuli originated from a baseline temperature of 32°C and each stimulus was terminated when the participant pressed the stop button according to the respective instructions. Detection thresholds for cold (CDT) and warmth (WDT) as well as pain thresholds for cold (CPT) and heat (HPT) were determined in triplicates with increasing or decreasing stimuli with a ramp slope of 1°C/s and interstimulus intervals of 4-6s and 10s, respectively. Thermal sensory limen (TSL) was assessed with six alternating ramped increasing and decreasing stimuli applied with a ramp slope of 1°C/s. Simultaneously, the number of paradoxical heat sensations (PHS) was assessed. Mechanical detection threshold (MDT) were tested as the sensation of light touch by determining the geometrical mean by a modified method of limits with five series of ascending and descending stimulus intensities (sub- and suprathreshold) using standardized von Frey hairs (0.25, 0.5, 1, 2, 4, 8, 16, 32, 64, 128, 256, 512 mN) (Optihair2-Set, MRC Systems GmbH, Heidelberg, Germany) with a blunted contact area of approx. 1 mm² to avoid nociceptor activation. Mechanical pain threshold (MPT), testing the detection of sharp, pricking, or stinging stimuli, was determined analogously using a set of 7 Pin-Prick stimulators with standardized stimulus intensities (8, 16, 32, 64, 128, 256, 512 mN) and a contact area with a tip diameter of 0.25mm (MRC Systems GmbH, Heidelberg, Germany). In addition, mechanical pain sensitivity (MPS) and dynamical mechanical allodynia (DMA) were assessed using the PinPrick stimulators in combination with allodynia testing equipment (customary bristle brush size 18, customary Q-tip, customary cotton wool) and each stimulus was

applied five times in a randomized order. Subsequently, wind-up ratio (WUR) was assessed using a single PinPrick stimulator (256 mN) with the help of a KorgMa 30 metronome (MRC Systems GmbH, Heidelberg, Germany). Vibration detection threshold (VDT) was measured in triplicate using a customary Rydel-Seiffert 64 Hz tuning fork (AESCULAP OF 33, AESCULAP Surgical Instruments, B. Braun, Melsungen, Germany) using as osseus protuberances the processus styloideus ulnae as well as the patella as recommended by the DFNS. Lastly, pressure pain threshold (PPT) was determined in triplicate using AlgoMed digital algometer (Medoc Ltd., Israel) and the corresponding software as stated above. Thresholds were measured at the thenar eminence and the quadriceps femoris muscle, respectively.

Raw data was processed to calculate each threshold according to the directives of the DFNS. Then QST data was stratified for age, gender, and area by calculating z-scores using the respective reference values. To allow direct interpretation of the sensory profile, algebraic signs were adjusted for each parameter. Gain of functions (GOF) were defined as z-scores above the 95% confidence interval (CI) and loss of functions (LOF) as z-scores below the 95% CI.

Assessment of Pain intensities, Psychometry, and Medical History

All participants were asked to rate their perceived pain intensities on a numerical rating scale (NRS) under resting conditions and stress-induced, such as perceived during mild exercise. NRS ranged from 0 defined as no pain, to 10 defined as the worst imaginable pain. In addition, participants received the German Pain Questionnaire (DSF) of the German Pain Association [10; 30] This questionnaire is extensively validated and is used as a standard pain diagnostics tool in Germany. It helps to asses not only biological data and a comprehensive medical history, but also data to further characterize the perceived pain as well as the current psychometry of the patient in a standardized manner. As a central tool, the questionnaire combines several validated scores. The German depression-anxiety-and-stress scale (DASS) [32], is used to investigate potential burden or co-morbidities with respect to depression, anxiety, and stress, respectively. Furthermore, to investigate the habitual well-being as well as the general health condition, the

DSF comprises the FW7 and the VR-12 [24] scores. In addition, it contains a comprehensive section of pain descriptions, such as occurrence, courses, duration, pain description list (Schmerzbeschreibungsliste (SBL)) [26], and grades of severity according to von Korff [45], amongst others.

Á priori sample size calculation and statistics

Á priori sample size was calculated using G*Power Version 3.1.9.6 for windows. We defined the level of significance $\alpha = 0.05$ and a power of 80 % assuming a large effect size. Based on these numbers, we calculated a sample size of $n = 17$ with an additional $n = 3$ for potential dropouts per group. As participants can retract their consent until publication, we recruited and measured all 20 per group.

The evaluation of QST measurements were calculated with Microsoft Excel 2010 for windows. All subsequent analyses of sensory data were done after stratification for age, gender, and body area, based on the calculated z-scores.

All statistical tests were performed using GraphPad Prism 6 for windows. Statistical significance was set at the level of $\alpha = 0.05$. Biometrical and psychometric data with continuous variables were compared using independent t-tests. Categorical data was tested via contingency tables by chi-square. Z-scores of QST measurements were tested with two-way repeated measures design analysis of variances (ANOVA), followed by Sidak's post hoc tests to correct for multiple comparisons. Due to technical issues we were not able to assess thermal thresholds in the thigh of one LiDo patient. All data of this patient were excluded from the statistical analysis. However, we decided to keep the data in the graphical representations, since thermal thresholds did not seem to be affected in LiDo patients.

To gauge the potential diagnostic ability of QST threshold assessment in the diagnosis of LiDo, we calculated receiver operating characteristic (ROC) curves [6] for single measurements at the lateral thigh and combinatory measurements at the hand dorsum and the lateral thigh as well as separate and combined measurements of PPT and VDT, respectively. All analyses were

conducted using z-score values of the control group versus z-score values measured in the LiDo group.

Results

Study population consisted of non-obese age- and WtHR-matched women with only minor comorbities.

The study was conducted in German and all 40 participants spoke the language on native speaker level. An overview of the descriptive biometrical data is given in table 1. We did not find a statistically significant difference with respect to age (ctrl: 27.15 ± 4.2 years, LiDo: 27.35 ± 4.4 years; p = n.s), height (ctrl: 169.3 ± 6.0 cm, LiDo: 165.7 ± 7.3 cm; p = n.s), weight (ctrl: 63.4 ± 7.7 kg, LiDo: 68.3 ± 11.1 kg; p = n.s.), and waist (75.2 ± 5.1 cm, LiDo: 76.3 ± 7.8 cm; p = n.s.). The waist to height ratio (WtHR, waist[cm]/height[cm]) was calculated and we did not find a statistically significant difference between the two groups (ctrl: 0.44 ± 0.03, LiDo: 0.46 ± 0.04; p = n.s.). As LiDo is a diet-unresponsive fat-distribution-disorder, a comparable metabolic state [31] is accompanied with a slightly higher overall body-mass index (BMI, weight[kg]/(height[m])^2) [9]. In agreement with this assumption, LiDo-patients showed a slight but statistically significant higher BMI compared to the controls (LiDo: 24.8 ± 2.9 kg/m^2, ctrl: 22.1 ± 2.4 kg/m^2, $p < 0.05$). BMIs of both groups were within the normal or slightly over-weight range [27].

Psychometric parameters and comorbidities were assessed using the DSF questionnaire. While all received the DSF, only the 14 LiDo patients providing the full information were analyzed. Each group comprised of two participants reporting mental or emotional strains with only negligible repercussions on the daily lives of the participants. Furthermore, three controls and two LiDo patients indicated hypothyreosis sufficiently medicated with replacement therapy. One participant of the control group reported mild asthma as well as one participant each of the LiDo group reported migraine and sinusitis, respectively. Two control participants and one LiDo patient indicated problems with reflux or gastritis. Endometriosis was diagnosed in two of the LiDo patients. There was one participant with focal nodular hyperplasia in the control group and another control participant reported peripheral nerve injury comprised a different dermatome than the

areas of interest for the QST measurement. A total of four participants (Ctrl: 1, LiDo: 3) reported orthopedical entities, such as recurrent backpain due to false posture or ruptured ligaments.

All LiDo patients were diagnosed as stage I or II [36] at least 6 months before the measurement (11.2 ± 6.6 years, range 0.5 – 27 years). They associated the manifestation of the disease with phases of hormonal changes, such as puberty, and 14 reported a familial history of LiDo with affected kin. All LiDo patients reported perceived chronic pain in the affected legs and in approx. 90% of patients the pain was present for 2 years or longer.

LiDo patients showed no signs of depression, anxiety, or stress and lacked indications for concerning mental abnormalities.

The DSF includes the "Depression, Anxiety, Stress Score (DASS)". All scores for both groups were in the normal range i.e. below the respective threshold values (dashed red lines) of 10 (depression, stress) or 6 (anxiety), respectively (Figure 1a). Nevertheless, while overall non-pathological, all scores were significantly higher in LiDo patients compared to controls with respect to depression (LiDo 5.57 ± 4.26 versus controls 2.4 ± 3.66), $t(32) = 2.33$, $p < 0.05$), anxiety (LiDo 2.86 ± 3.03 versus controls 1 ± 1,3), $t(32) = 2.45$, $p < 0.05$), and stress (LiDo 7.29 ± 4.34 versus controls 3.1 ± 2.47), $t(32) = 3.58$, $p < 0.01$).

The DSF includes the veterans RAND-12 (VR-12) score to assess the general health condition. The score is subdivided into a "physical compartment summary (PCS)" and a "mental compartment summary (MCS)". Scores of both groups show normal values above the cut-off value (dashed red line, Figure 1b). While non-pathological, the comparison between the two groups indicated a statistically significantly reduced score in the PCS in the LiDo group (43.78 ± 8.69) compared to the control group (54.25 ± 7.69), $t(30) = 3.59$, $p < 0.01$. For the MCS, the LiDo group showed slightly abnormal values being below the cut-off value of 43. Nevertheless, we did not find a significant difference in MCS between the groups (Ctrl: 48.38 ± 14.56, LiDo: 40.99 ± 15.46), $t(30) = 1.38$, $p > 0.05$).

Furthermore, the DSF includes the FW7 questionnaire to assess the habitual well-being (see figure 1c). The score does not contain a cut-off value but represents rather a continuous scale (0-35) with higher scores indicating higher well-being. This questionnaire was developed specifically for chronic pain patients of any diagnosis. In general, scores from the mid-range and up can be considered as normal. We found a mid-range score in the LiDo group and a high-range score in the controls. Despite the significantly reduced score in the LiDo group (17.64 ± 7.84) compared to the controls (29.94 ± 5.81), $t(30) = 5.1$, $p < 0.0001$, both scores indicate normal habitual well-being in both cohorts.

LiDo patients report severe persistent pain with circadian fluctuations described with somatic terms.

All participants were asked to rate their pain intensity during resting as well as during stress such as mild exercise. Pain intensity was indicated on a numerical rating scale (NRS), where 0 indicates no pain and 10 indicates the worst pain imaginable (figure 2a). Control participants did not report noticeable pain with the exception of two participants with very mild stress-induced pain perceptions due to occasional non-chronic posture-induced back pain. In contrast, LiDo patients reported pronounced pain at resting conditions (6 ± 2.18), $t(32) = 12.37$, $p < 0.0001$, and increased stress-induced pain intensities (7.43 ± 1.91), $t(32) = 11.96$, $p < 0.0001$.

All LiDo patients reported an increase in pain intensities throughout the day, starting at around early afternoon and culminating in the evening, indicating a distinct circadian pattern (figure 2b). The pain reports indicate highly divergent individual pain experience with various degrees of oscillation and/or attacks. All but 4 reported continuous pain.

All patients were asked to describe their pain in their own words. Around 80% indicated pressure pain, followed by adjectives such as heaviness (57%), dragging or stinging (each 29%). To further objectify this, we used the pain description list (Schmerzbeschreibungsliste (SBL) [26] to capture the emotional or affective part (SBL-A) on one hand and the somatic part (SBL-S) on the other hand (see figure 2c). In our study population the affective score (SBL-A) remained considerably

below the threshold value, while the sensory score (SBL-S) presented higher values, indicating a subordinated role for the affective component and the LiDo pain in the patient cohort to be of somatic nature.

The von Korff grading system captures the severity of pain as a function of intensity and disability [45] (see figure 2d). The grades are defined as 0 for no pain, 1 for low pain intensity and low disability, 2 for high pain intensity with low disability, 3 for high pain-related disability that is moderately limiting, and grade 4 for high pain-related disability that is severely limiting. In general, we see a significant difference between both groups ($\chi^2(4) = 25.98$, $p < 0.0001$), with lower grades of severity (≤ 1) in the control group and higher grades (≥ 1) in the LiDo patients. In general, LiDo pain is reported to be moderately limiting; however, in two cases severely limiting.

Normal sensitivity thresholds for all LiDo patients and controls measured at the dorsum of the hand

Questionnaire-based pain measurements are prone to be influenced by psychosocial aspects. To objectify the sensory input, we performed a Quantitative Sensory Testing (QST) according to the protocol of the DFNS with thresholds being determined in a graded manner by averaging over multiple super- and supra-threshold stimuli for each single person [29; 34; 37; 38]. The QST protocol tests 7 thresholds, which allows access to 13 aspects of primary afferent neuron physiology as listed in figure 3.

First, accuracy of the approach was confirmed by measuring controls at the dorsum of the hand. Comparison with control data from the DFNS-database confirmed threshold Z-scores for all parameters to remain in the normal range within the 95% CI (-1.96 to 1.96), indicating proficient use of the experimenter of the QST-protocol, absence of generalized pain, as well as normal sensory profiles in all participants at the dorsum of the hand (figure 3a). Similarly, all LiDo patients showed threshold values in the normal range similar to non-LiDo controls (figure 3a). A repeated measures ANOVA followed by Sidak's post hoc test showed no significant difference between

both groups in any of the parameters assessed at the dorsum of the hand (figure 3a), $F(1, 418) = 0.0002$, $p > 0.05$.

Selectively decreased threshold for pressure pain and increased threshold for vibration detection at the lateral thigh of LiDo patients

Next, measurements were conducted at the lateral thigh as one of the areas with the greatest sensation of pain (see figure 3b). Z-scores of the control group remained in the normal range within the 95% CI, with the exception of a slightly increased value for the pressure pain threshold. The meaning of this remains questionable, as the DFNS controls, which establish the z-score, were not measured at the thigh but at the foot. Also for the LiDo group, QST measurements were in the normal range for most test stimuli with two exceptions: 1) value for the pressure pain threshold were strongly increased (see figure 3c, PPT), indicating pain hyper-responsiveness; 2) values for the vibration detection threshold were strongly decreased (figure 3c, VDT) suggesting reduced sensitivity to vibration. Repeated measures ANOVA followed by Sidak's multiple comparison post hoc test revealed a significant difference between both groups ($F(37, 370) = 2.485$, $p < 0.0001$) in the PPT ($p < 0.0001$, 95% CI = -3.442, -1.371) and the VDT (($p < 0.0001$, 95% CI = 1.203, 3.274).

Assessment of single PPT or VDT values shows high sensitivity and selectivity to identify participants as LiDo patients.

QST-measurements establish objectified threshold values for physiological sensory modalities. A full QST-protocol requires about 30 minutes of data acquisition for each area. Accordingly, such measurements are mostly performed within scientific studies. Our data now indicate changes of only two of the measured 13 values. Thus, next we investigated whether consideration of only those two parameters allows for a reliable reassignment of all 40 measured women as either LiDo patient or normal-control. For this, a "receiver operator characteristic (ROC)" analysis for sensitivity and specificity of such an assignment was performed. First, we tested if only using either the values for the PPT or alternatively only using the VDT would allow to correctly identify

the a participants as either LiDo patient or control. Each parameter alone showed promising diagnostic ability to distinguish LiDo and control participants, assigning in the best case 90.75 % (PPT) and 86.38 % (VDT) of the measured women correctly as LiDo or control (PPT: AUC = 0.9075, $p < 0.0001$; VDT: AUC = 0.8638, $p < 0.0001$).

Combination of PPT and VDT values shows higher sensitivity and selectivity to assign participants as LiDo patients.

Next we asked whether the evaluation of a combined value of PPT and VDT potentially allows an even better identification of single individuals as either LiDo patient or control. For this, we defined the absolute value of the sum of the z-scores of the PPT and VDT measured at the lateral thigh as new test and performed another ROC analysis. Combining both parameters increased the diagnostic ability to even 94.25 % correct assignement as LiDo or control as shown in figure 4b (AUC: 0.9425, $p < 0.0001$).

Combination of measurements of PPT-hand and PPT-thigh or of VDT-hand and VDT-thigh does not increases the sensitivity and selectivity to assign participants as LiDo patients further.

Since we measured all QST parameters at the thigh as well as the hand as an intra-individual control site, we tested whether a combination of the QST measurements taken at the thigh with the ones taken at the hand allows an even more sensitive and selective assignment of measured individuals as LiDo patients or controls. For this, we subtracted the absolute z-score hand-values from the respective thigh-values of the same individual for PPT as well as separately for VDT, respectively ($\Delta_{(parameter)}$ = z-score$_{(thigh)}$ – z-score$_{(hand)}$). This did not increase the sensitivity and selectivity to assign measured women as LiDo or control (figure 4c , PPT: AUC 0.885, $p < 0.0001$; VDT: 0.935, $p < 0.0001$).

Integration all 4 measurements (PPT-hand, PPT-thigh, VDT-hand, and VDT-thigh) shows the best sensitivity and selectivity to identify participants as LiDo patients or controls.

Last but not least, we investigated the ability of a combination of all four measurements into one test score, namely PPT and VDT, and each of them measured at the hand dorsum and at the

lateral thigh of each individual for its sensitivity and selectivity to identify the measured women as LiDo or control, respectively (figure 4d).The combined test score is defined by $\Delta_{(\text{PPT-thigh} - \text{PPT-hand})} + \Delta_{(\text{VDT-thigh} - \text{VDT-hand})}$. Of all ROC analyses this approach resulted in both, best sensitivity and best specificity, identifying 96.5 % of the measured individuals correctly as LiDo patient or as control (AUC = 0.965, $p < 0.0001$). Table 2 provides a list with respective sensitivity-specificity pairs for exemplary criterion values, indicating reliable true positive and negative rates, respectively.

Taken together, we conclude from this result that a joint measurement of z-scores of only PPT and VDT at the dorsum of the hand and the lateral thigh shows promising power for the differentiation of LiDo versus control. This suggests that one may reduce the full QST-protocol of 7 measurements at two different sites to just these two measurements thereby reducing the time from about 1-1.5 h to about 10 minutes while maintaining a very high sensitivity and selectivity for the identification of LiDo patients on a single patient basis.

Discussion

Pain is one hallmark of LiDo. We aimed to objectify the experience of LiDo-pain and of potential alterations of pain-inducing or non-painful sensations. This may give insight into the pain ethiology but also may help the development of novel diagnostic tools.

LiDo shows a broad phenotype. It is differentiated by appearance of the skin surface as stage I, II, or III. In addition, patients vary from normal to severely overweight. We focused on normal to moderately-overweight patients of LiDo stage I or II. Such focus helps to reduce patient-variability, avoids a potential influence of coinciding obesity, and thus serves as sensitive mechanistic analysis. Our cohort comprised of 20 non-obese LiDo patients and 20 non-obese age-matched control participants. Both groups showed comparable weight, height, waist, and WtHR, respectively. Currently research transitions from BMI to WtHR data to achieve metabolism-oriented group matching for this fat distribution-disorder [1; 9; 15; 41; 48]. Accordingly, in our cohort the BMI was slightly increased in the LiDo group while the WtHR remained similar between the groups [23; 27].

All participants reported minor comorbidities such as orthopedical entities or hypothyreosis. Hypothyroidism has been reported as one of the major comorbidities in LiDo [5]. In our cohort, prevalence of comorbidities including hypothyreosis are not different from the general population [49] and thus are negligible in the context of this study. Some of our participants reported occasional back-pain or migraine. Our study criteria exclude patients only if diagnosed chronic pain patients. Thus, these participants remained included. As occasional back pain is widespread, our cohort may represent well the general population.

LiDo pain is mostly simply referred to as “pain”. To understand potential underlying mechanisms, it is of importance to differentiate pain by e.g. quantity of experience, location, duration, dynamic, mental state, and sensory thresholds. Such differentiation is only emerging. Similar to reports by others [11], our LiDo patients reported persistent pain with circadian fluctuations in the legs. In contrast to reports by Chakraborty et al. [11], self-reported pain of stage I and II patients was

severe. Pain perception depends among others on the general well-being and mental status [7]. Accordingly, psychometry was assessed using the DFS. Both groups reported normal scores for depression, anxiety, stress (DASS questionnaire), PCS (VR-12 questionnaire), and general well-being, except for a marginally reduced VR-12 MCS score for LiDo patients. Conclusively, we do not have any indication that LiDo patients in general show psychometric abnormalities as suggested by others [14]. While normal in general, LiDo patients were considerably more burdened than controls. If this reflects mostly the experienced chronic pain or e.g. stigmatization, reduced self-appraisal, or self-acceptance in a rather inflated beau ideal driven society has not been detailed [13]. But LiDo patients have in average lower quality of life values with respect to social, mental, and physical functioning [39]. Such psychological burden of LiDo is often reported to be aggravated by misleading treatment advice of weight reduction contributing to a negative self-image. The verbal description of pain with adjectives can point to somatic versus emotional contributions to pain [17]. Corroborating reports by others [21; 40], we found LiDo pain to be experienced as a localized somatic rather than a psychosomatic aversive event.

So far, it has not been attempted to differentiate the pain according to thermal, mechanical, pressure, vibrational, and/or alterations of other sensory modalities. We performed standardized QST measurements assessing 13 different sensory thresholds according to the protocol of the DFNS [29; 34; 37; 38] as this may give insight into the underlying mechanism. Our QST data are always compared to many thousand QST control profiles in the DFNS database. As expected, sensory thresholds were normal in the non-affected hands. This result also served as quality assurance for a reliable performance of the measurements. We found a significant pain sensitization for pressure pain at the lateral thigh. Furthermore, a significant increase of vibration detection thresholds was identified in LiDo patients. The slightly increased PPT z-scores of control participants may reflect, that z-scores are computed in relation to the DFNS-standard control, which is the dorsum of the foot [29; 34; 37; 38]. In contrast to the slight deviation of controls, the PPT value of LiDo patients shows a pronounced increase. An attribution to an increase amassing

of adipocytes at the thigh appears unlikely. Indeed, increased adipose tissue should rather dampen pressure transmission and thus should rather render those sites less sensitive [18], which is not the case in our LiDo cohort.

QST was established to assess disease modalities and affected sensory fiber types. A QST profile with increased PPT and lowered VDT as only aberrations has not been reported. Thus, what causes this altered sensory fiber physiology remains speculative [4; 43; 44]. Pressure pain is mostly transmitted via small or medium diameter C- or Aδ-fibers [33]. Vibration stimuli are conveyed via large diameter rapidly conducting Aβ-fibers [33]. All other QST measures but PPT and VDT are normal. The psychometric data do also not indicate neuropathic pain. This does rather indicate normal sensory innervation, normal stimulus detection and transmission, as well as normal central integration. This also excludes classical inflammatory sensitization, as there is no sign of e.g. mechanical hyperalgesia or allodynia in the measured skin. Nevertheless, as all thresholds are normal in the hand, a systemic driver of pain may be excluded as well. Chakraborty and colleagues reported a dynamic mechanical allodynia, which was in contrast to their patient pain-rating, and did not identify a clear neuropathic component [11]. We did not see dynamic mechanical allodynia in our cohort, assessing allodynia using a brush, cotton wool, and a q-tip. In contrast to Chakraborty, none of our standardized von Frey filaments induced pain perception, even though our filaments exerted slightly more force than those used by Chakraborty. In contrast to Chakaraborty, our sensory testing was in line with the patients' pain reports. Thus, our QST data point to a local, modality and fiber-subtype specific alteration.

This study is designed as proof of principle study testing the full time-consuming QST battery. The result indicates only PPT and VDT to be altered. Thus, it is attractive to explore in a post hoc testing, if just these two values may be enough to assign the measured profiles as LiDo or control. Indeed, ROC analyses revealed a highly promising power for such an assignment. This suggests that one may reduce the full QST-protocol to the measurement of only two parameters at two distinct sites reducing the assessment time to approximately 10 minutes. Due to this time

economy in combination with requirements of only a tuning fork and a pressure algometer, this method may serve as a simple, time economical, and cheap bedside test. We propose to measure this PVTH (PPT, VDT, Thigh, Hand) score according to the DFNS protocol for highest sensitivity and specificity. Particular attention should be paid on the order of measurement since the validity of QST parameters has been shown to be crucially dependent on the correct order [22]. Therefore, first VDT and then PPT should be measured and z-scores calculated as recommended by the DFNS. Both thresholds should be assessed first at the hand dorsum and subsequently at the lateral thigh, respectively. Which score value then allows the best differentiation is currently tested on an independent larger cohort.

As proof of principle study, one limitation is the relatively small sample size. Especially ROC analyses for testing diagnostic abilities rely on larger sample sizes. Nonetheless, we think our cohort provides good indication for the diagnostic potential of a PVTH score. A further limitation is the focus on normal to slightly overweight LiDo patients. Whether PVTH scores are different also in obese LiDo patients is currently under investigation. Nonetheless, assessing both sensory thresholds would be a major help in LiDo differential diagnoses even if this turns out to be only valid in non-obese patients. These patients rather represent the majority of women at the beginning of disease manifestation. Especially at this stage, a prompt and reliable diagnosis is crucial to alleviate ample suffering due to prolonged time until diagnosis.

Taken together, we found no evidence for mental strains in normal to moderately overweight LiDo patients indicating absent psychosomatic tendencies and rather the presence of somatic correlates for the perception of pain. Furthermore, we comprehensively provided a distinct sensory profile with decreased pressure pain and increased vibration detection thresholds in the affected lateral thigh but not the pain-free hand. We propose the assessment of both, VDT and PPT, at the dorsal hand and the lateral thigh, respectively, as a PVTH-score with a promising potential for LiDo diagnosis. Certainly, this has to be validated in a larger and independent cohort, which is the object of future research.

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Figure legends

Figure 1: Psychometry of the participants as measured by the DSF. Dashed lines indicate cut-off values separating scores considered as normal or anormal, respectively. **a)** All scores of the depression-anxiety-stress scale (DASS) remained below the cut-off values and thus are considered as normal. **b)** Results for the general health condition (veterans RAND-12 (VR12)) questionnaire with respect to the "physical compartment summary (PCS)" and "mental compartment summary (MCS)". Scores above dashed lines are considered as normal values. We found normal scores for both groups in the PCS, MCS scores slightly below the threshold value in LiDo patients indicating the presence of minor mental burden. **c)** Results for the habitual well-being (FW7 questionnaire) with higher scores indicating more well-being. We found a reduced score in LiDo patients; however, still in the mid-range of the scale, indicating normal habitual well-being values for patients with chronic pain. (All values are displayed as mean + standard deviation. Ctrl n = 20, LiDo n = 14).

Figure 2: Characterization of LiDo pain as measured by the DSF. a) Pain intensity ratings on numerical rating scale (NRS;0 = no pain, 10 = worst imaginable pain) under resting conditions and stress-induced, e.g. during mild exercise. LiDo pain ratings were significantly increased compared to the control group, where pain was virtually absent. (Ctrl n = 20; LiDo n = 20; independent t-test; **** $p < 0.0001$). **b)** Pain profiles (modified from [10]) as described by LiDo patients with circadian fluctuations. **c)** Results for the German version of the Pain Description List (SBL),subdivided into an affective (SBL-A) and somatic (SBL-S) part. Values above the dashed line indicate a pathologic SBL-A of increased affective pain perception. This was not the case in our population of LiDo patients. (n = 14). Furthermore, the higher SBL-S score indicated a rather somatic nature of LiDo pain. **d)** Grades of severity according to von Korff (0: no pain; 1: low pain intensity; low disability; 2: high pain intensity; low disability; 3: high pain-related disability;

moderately limiting; 4: high pain-related disability; severely limiting). (Ctrl n = 20; LiDo n = 14; chi square test; **** $p < 0.0001$).

Figure 3: Mean QST Sensory Profiles. a) Mean QST sensory profiles of control and LiDo participants measured at the dorsum of the hand. Values between -1.96 and 1.96 are considered normal. **B)** Mean QST sensory profiles of control and LiDo participants measured at the lateral thigh. We found significantly increased PPT and decreased VDT values, respectively, in LiDo patients **c)** Display of single participant data of controls and LiDo patients measured at the lateral thigh for PPT and VDT. (CDT cold detection threshold, WDT warmth detection threshold, TSL thermal sensory limen, CPT cold pain threshold, HPT heat pain threshold, PPT pressure pain threshold, MPT mechanical pain threshold, MPS mechanical pain sensitivity, WUR wind-up phenomenon, MDT mechanical detection threshold, VDT vibration detection threshold, PHS paradoxical heat sensations, DMA dynamical mechanical allodynia). (Ctrl n = 20, LiDo n = 20 (except thermal thresholds at the lateral thigh: n = 19 (see results section for explanation)), two-way repeated measures ANOVA, **** $p < 0.0001$)

Figure 4: ROC analyses for diagnostic ability investigation of assessed QST z-scores. a) ROC analyses of PPT and VDT measured at the lateral thigh in control participants and LiDo patients. Each parameter alone showed promising diagnostic ability to distinguish both groups of our study population. **b)** ROC analysis of the sum absolute values of both parameters on single patient level. Assessment of both parameters increased the diagnostic ability. **c)** Intraindividual control measurements are considered by absolute value subtraction of hand measurements from measurements of the thigh for each parameter. Again, both parameters showed promising diagnostic ability. **d)** addition of both values calculated in c) showed the highest diagnostic potential in terms of sensitivity and specificity

Tables

Table 1: Biometrical data

	Ctrl		LiDo		*p*
	Mean +/- Sd	range	Mean +/- SD	range	
age [years]	27.15 +/- 4.2	20 - 37	27.35 +/- 4.4	23 - 40	n.s.
height [cm]	169.3 +/- 6.0	157 - 179	165.7 +/-7.3	152 - 175	n.s.
weight [kg]	63.4 +/- 7.7	48 - 76	68.3 +/- 11.1	54 - 88	n.s.
waist [cm]	75.2 +/- 5.1	60 - 80	76.3 +/- 7.8	66 - 99	n.s.
WtHR	0.44 +/- 0.03	0.38 - 0.5	0.46 +/- 0.04	0.41 - 0.57	n.s.
BMI [kg/cm²]	22.1 +/- 2.4	18.8 - 27.6	24.8 +/- 2.9	20.2 - 28.9	< 0.05

Table 2: Exemplary sensitivity-specificity threshold value pairs

treshold value	**sensitivity** [%]	**95% CI**	**specificity** [%]	**95% CI**	**likelihood ratio**
> 1.907	95	75.13% to 99.87%	40	19.12% to 63.95%	1.583
> 2044	95	75.13% to 99.87%	45	23.06% to 68.47%	1.727
> 2938	95	75.13% to 99.87%	85	62.11% to 96.79%	6.333
> 3140	95	75.13% to 99.87%	90	68.30% to 98.77%	9.500
> 3302	95	75.13% to 99.87%	95	75.13% to 99.87%	19.000
> 3340	95	75.13% to 99.87%	100	83.16% to 100.0%	

combinatory measurements of PPT and VDT at the hand dorsum and the lateral thigh

Figures

Figure 1

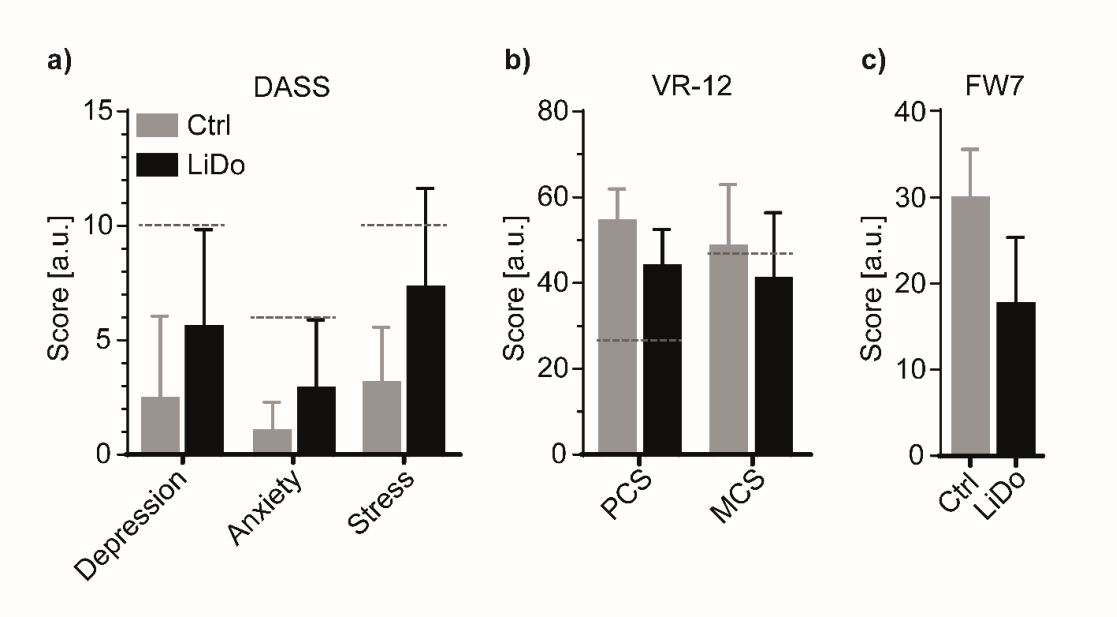

Figure 2

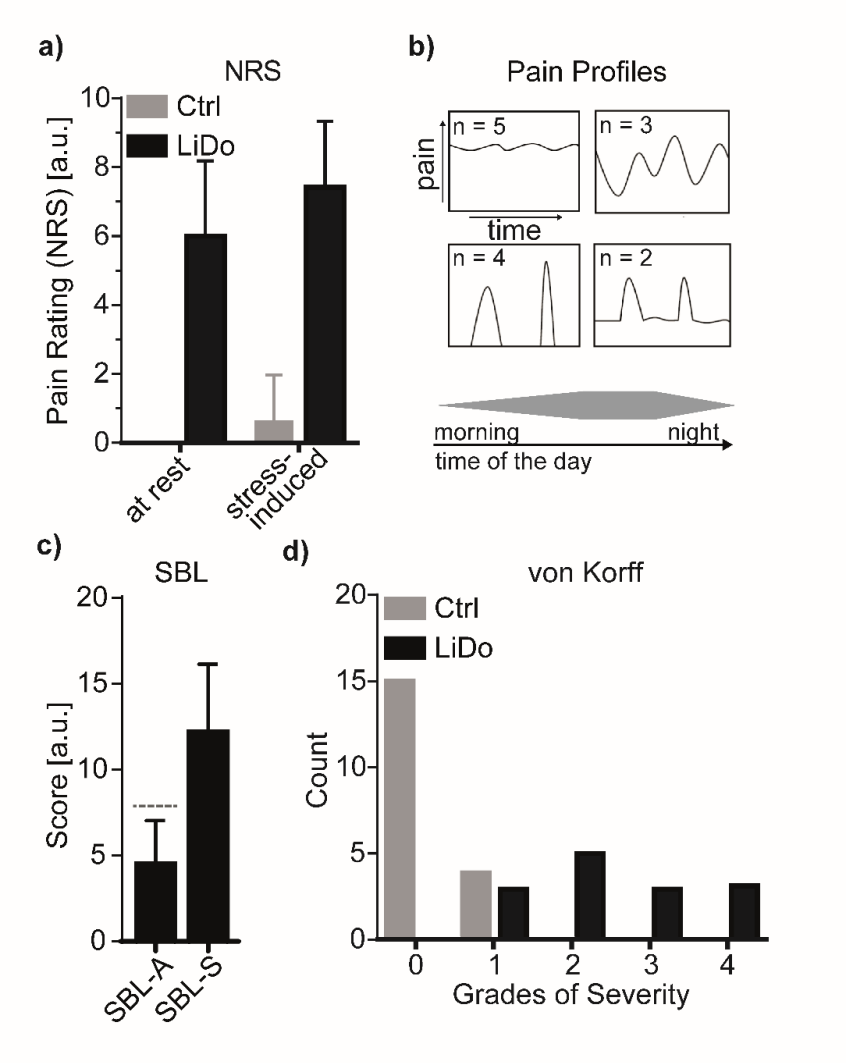

Figure 3

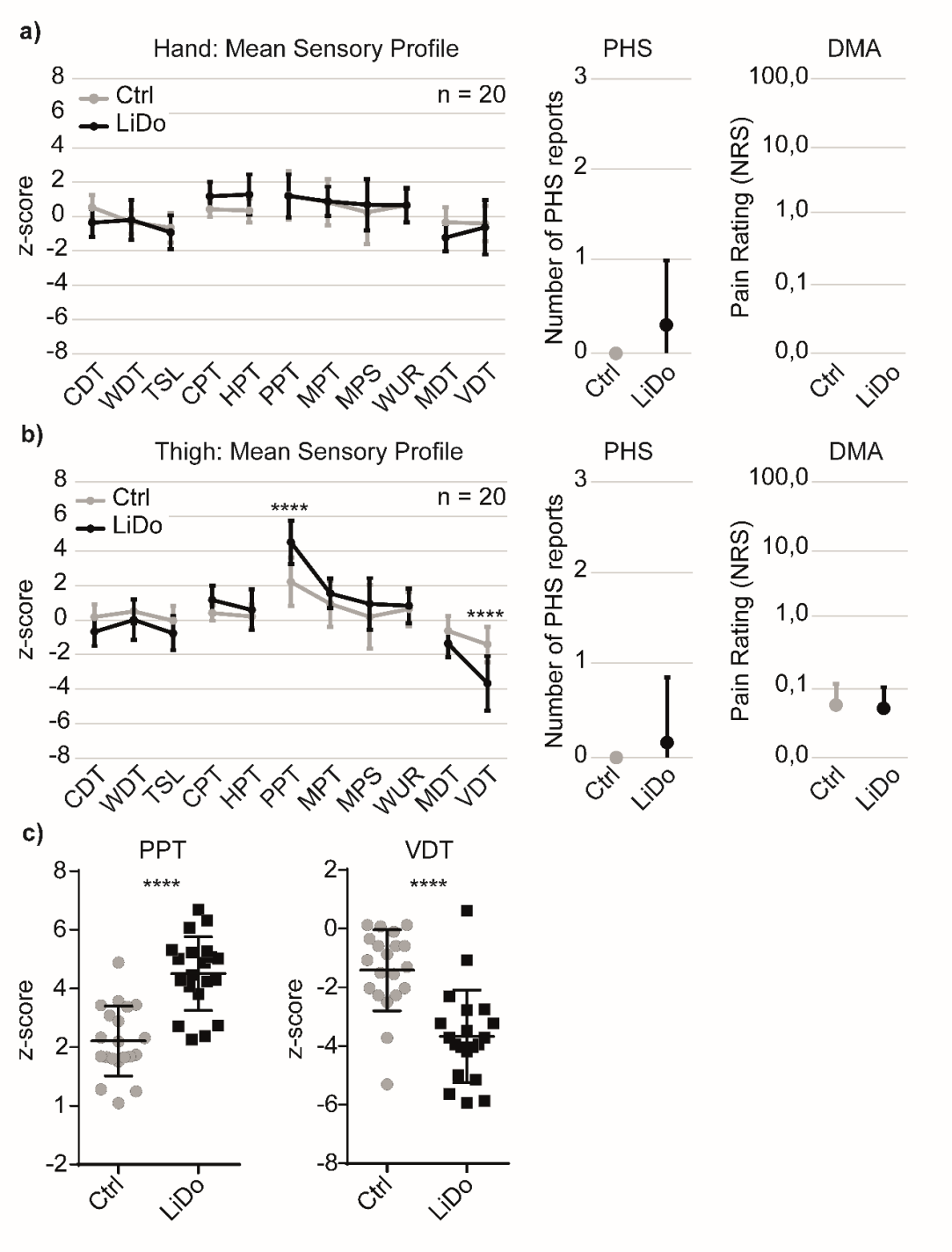

Figure 4