Detection sensitivity of ultrasound scanning vs. clinical examination for insulin injection-related lipohypertrophy

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To the Editor: Lipohypertrophy (LH) is the most common local complication caused by multiple overlapping insulin injections. Clinically, LH manifests as prominent and/or thickened tissue at injection or infusion sites, sometimes resulting in lump formation under the skin. Histologically, LH is characterized by decreased vascularity, fibrosis, and adipocyte enlargement and proliferation in the subcutaneous tissue at insulin injection sites. Because of this, the existing screening methods for LH are mainly based on clinical examination and ultrasound scanning (USS). A recent systematic review revealed that only limited information is available for detection sensitivity among the different methods used to identify LH to date. Thus far, the gold standard examination for LH diagnosis remains debatable and there has been insufficient research on which patients require both kinds of examination. Currently, the detection sensitivity of USS vs. clinical examination for LH has not been reported in large sample-based studies. The present study aimed to compare the detection accuracy between USS and clinical examination using a large patient cohort and to determine the influencing factors for inconsistent detection results of LH between the two methods.

This cross-sectional study was performed on 382 patients on daily insulin therapy involving multiple injections into their abdomen only at the National Endocrine and Metabolism Centre in Jiangsu, China, from March 2018 to March 2020. The inclusion criteria were age >10 years; diagnosis of type 1 or type 2 diabetes mellitus according to the diagnostic criteria and classification criteria for diabetes published by WHO in 1999; insulin only given to the abdomen; current treatment with a minimum of one insulin injection daily or insulin pump for at least 1 year; ability to understand and cooperate with the research; lack of other malignant disease or any disease-causing wasting. The exclusion criteria were prescription of glucagon-like peptide-1 agonist; dermatitis or any other cutaneous disease.

All patients completed a validated questionnaire-based interview with the help of a specifically trained nurse. Recorded parameters included demographic and clinical information. The demographic data included age, sex, and degree of education. The clinical information included type of diabetes, diabetes duration, insulin exposure duration, body mass index (BMI), insulin injection tool, needle length, daily insulin dose, glycosylated hemoglobin (HbA1c), reuse of needles, frequency of needle reuse, and method of site rotation. All of the personal information was recorded and kept confidential. Patients were evaluated for LH by clinical examination and USS. The examiners were blinded to the participants’ data collected in the previous stage. On both clinical examination and USS, LH was assessed as either “present” or “absent.” Before study participation, written informed consent was received directly from patients aged >18 years and received from both the patients and their parents for those aged <18 years. The study was approved by the Research Ethics Committee of the First Affiliated Hospital of Nanjing Medical University (No. 2019-SR-268).

Continuous variables were reported as mean ± standard deviation, and categorical variables were summarized as rate or percentage. First, the detection consistency between clinical examination and USS assessments was estimated by McNemar test. Cohen kappa statistic was used to evaluate the agreement between the two detection methods. Second, the sensitivity and specificity for each method vs. the other were calculated. Finally, the correlations between different variables were tested and independent variables that influenced inconsistent detec-
tion results of LH between clinical examination and USS were determined using a binary logistic regression model. The odds ratio (OR) and 95% confidence interval (CI) were used to report the results. All data were analyzed using SPSS version 22.0 software (IBM Corp., Armonk, NY, USA). Values of \( P < 0.050 \) were considered to indicate statistical significance.

Of 400 patients initially included in the study, 382 successfully completed the study. The general information of the patient is listed in Supplementary Table 1, http://links.lww.com/CM9/A753. LH was detected using USS in 333 participants (87.2%). In contrast, LH was detected by clinical examination in 279 patients (73.0%). Among the 333 participants who were diagnosed with LH using USS, 263 were confirmed and 70 were misdiagnosed by clinical examination. Among 49 participants with negative results for LH detection by USS, 16 were diagnosed with LH by clinical examination. McNemar test showed a significant difference in LH detection results between the two methods (\( \chi^2 = 16.000, P < 0.001 \)). The agreement for the existence of LH determined by USS and clinical examination was fair, with a Cohen \( k \)-value of 0.315 (SE = 0.05, \( P < 0.001 \)). Compared with clinical examination as the standard, the sensitivity and specificity of USS were 94.3% and 32.0%, respectively. Relative to USS as the standard, the sensitivity and specificity of clinical examination were 79.0% and 67.3%, respectively. When compared with one another, USS had higher sensitivity and tended to detect more LH, and thus its missing rate was relatively low despite the time and money consumption. Meanwhile, clinical examination was easy and convenient to operate and had high specificity associated with a low misdetection rate.

To further analyze the influencing factors for inconsistent results between clinical examination and USS in the detection of LH, the five variables with significant differences in univariate analysis (age, diabetes duration, insulin exposure duration, BMI, and frequency of needle reuse; \( P < 0.050 \) for all) were entered into a binary logistic regression model. Insulin exposure duration (OR: 0.860, 95% CI: 0.80–0.93, \( P < 0.001 \)), overweight (BMI: \( 25.0–29.9 \) kg/m\(^2\); OR: 1.360, 95% CI: 1.03–1.79, \( P = 0.032 \)), and obesity (BMI: \( \geq 30.0 \) kg/m\(^2\); OR: 2.810, 95% CI: 1.07–7.29, \( P = 0.036 \)) were significantly associated with inconsistent results between clinical examination and USS in the binary logistic regression model [Table 1]. The present results showed that increased duration of insulin therapy was associated with a decreased rate of inconsistent detection of LH by clinical examination and USS. Although many studies have investigated the influence of insulin therapy duration on the development of LH using clinical examination, the findings of these studies were inconsistent. Our study indicated that patients who had received insulin therapy for a short duration were more likely to have different results for detection of LH, which may have resulted in conflicting results regarding the duration of insulin therapy and LH.

As another finding of the present study, inconsistent detection results of LH by clinical examination and USS were associated with BMI. LH was more difficult to detect by clinical examination in overweight patients, especially obese patients. These findings may have arisen through the positive correlation between BMI and subcutaneous fat thickness, especially for abdominal LH. Ji et al.\(^{11} \) surveyed insulin-injecting Chinese patients in four cities and found that 97.5% of these patients injected insulin into the abdomen. Patients often choose the abdomen as an injection site for convenience and faster absorption of insulin, which may further increase the difficulty of clinical detection of LH in overweight patients.

As LH will bring great harm to insulin injection patients, we believe that every LH should not be missed diagnosis. Also, it is important that we discover these sites early so as to let them disappear slowly when the degree of LH is not that serious.\(^{24} \) Another study by our team has shown that subclinical LH (a lesion meeting ultrasonic criteria for LH that was not detected by inspection and palpation) is related to glycemic control deterioration.\(^{3} \) For diabetes managers, it is also very important to master the influencing factors of LH.\(^{4} \) After the detection of LH, prevention and appropriate follow-up should take the first place in the management of these patients.\(^{5} \)

To date, USS and clinical examination are the only two methods commonly used to diagnose LH and there is no consensus on which method is the gold standard. Therefore, we assigned the gold standard to each of these methods while comparing the sensitivity and specificity between the two modalities. Further studies are needed to confirm the gold standard method for LH diagnosis in the future.

| Parameter                        | \( \beta \) | OR   | 95% CI of OR | \( P \) values |
|----------------------------------|------------|------|--------------|---------------|
| Age                              | 0.007      | 1.007| 0.99–1.02    | 0.390         |
| Diabetes duration                | –0.029     | 0.970| 0.93–1.02    | 0.248         |
| Insulin exposure duration        | –0.153     | 0.860| 0.80–0.93    | <0.001        |
| BMI                              |            |      |              |               |
| <18.5 kg/m\(^2\)                |            |      |              |               |
| 18.5–24.9 kg/m\(^2\)            | –0.161     | 0.850| 0.37–1.95    | 0.702         |
| 25.0–29.9 kg/m\(^2\)            | 0.305      | 1.360| 1.03–1.79    | 0.032         |
| \( \geq 30.0 \) kg/m\(^2\)      | 1.035      | 2.810| 1.07–7.29    | 0.036         |
| Frequency of needle reuse        | –0.021     | 0.979| 0.93–1.03    | 0.401         |

\( \beta \): Coefficient; BMI: Body mass index; CI: Confidence interval; LH: Lipohypertrophy; OR: Odds ratio.
To conclude, USS and clinical examination have their own advantages for detecting LH and both methods are recommended whenever possible. Given the economic cost and need for technical expertise, the combined approach would be most beneficial for those who have received insulin therapy for a short duration and those who are overweight or obese to avoid a missed diagnosis of LH.

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Conflicts of interest

None.

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