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● *Original Contribution*

ULTRASONOGRAPHY IMPROVES GLYCEMIC CONTROL BY DETECTING INSULIN-DERIVED LOCALIZED AMYLOIDOSIS

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Abstract—We examined the feasibility of ultrasound diagnosis of insulin-derived localized amyloidosis (IDLA). In addition to ultrasound detectability and findings, the insulin absorption rate, insulin dosage and hemoglobin A1c (HbA1c) levels before and after shifting the insulin injection site were investigated for 22 cases of IDLA. The detectability of IDLA on ultrasound was 100%; 59.1% was palpable lumps and 40.9% was not palpable. The palpable type had lower echo intensity and were harder than the non-palpable type. Blood flow decreased in IDLA, especially in the palpable type. IDLA, especially the palpable type, had a low insulin absorption rate. HbA1c level and insulin dosage decreased after shifting the injection site. The palpable type had more insulin reduction than the non-palpable type. Characteristic ultrasound images of IDLA were acquired. As the non-palpable type could be identified by ultrasound, its diagnosis encourages changing the insulin injection site; hence, ultrasound diagnosis of IDLA can enhance insulin treatment. (E-mail: kikuchim@sapmed.ac.jp) © **2017 World Federation for Ultrasound in Medicine & Biology.**

Key Words: **Insulin-derived localized amyloidosis, Ultrasound, Insulin injection site, Palpable type, Non-palpable type, Insulin absorption, Hemoglobin A1c, Insulin treatment.**

INTRODUCTION

Subcutaneous lesions occur at the injection site of patients with diabetic patients using insulin at a frequency of 44.4% (258/581) to 29.9% (20/67) (Ishii et al. 2015; Yamashiro et al. 2015). These subcutaneous lesions are usually caused by lipohypertrophy resulting from the fat-increasing action of insulin. In addition, Dische et al. (1988) reported that some subcutaneous lesions might also be insulin-derived localized amyloidosis (IDLA). Later, IDLA was referred to as an insulin ball by Nagase et al. (2009), and these lesions became widely known. Many researchers have reported the characteristics of IDLA related to decreases in insulin absorption, poor glycemic control by continuous insulin injection (Albert et al. 2007; Bernárdez et al. 2015; Ciin et al. 2005; Dische et al.1988; Endo et al. 2010; Grunes et al. 2015; Kudo-Watanuki et al. 2012; Kusuki et al. 2015; Lonsdale-Eccles et al. 2009; Nagase et al. 2009, 2014; Shikama et al. 2010; Sie et al. 2010; Swift et al. 2002; Yabe et al. 2015; Yoshizaki and Honda, 2012; Yumlu et al. 2009) and a vicious cycle of poor glycemic control despite increased doses of insulin (Bernárdez et al. 2015; Grunes et al. 2015; Gupta et al. 2015; Kusuki et al. 2015; Nagase et al. 2014; Shikama et al. 2010; Yabe et al. 2015; Yoshizaki and Honda, 2012). Therefore, shifting the injection site away from an IDLA lesion improves control of diabetes.

Insulin absorption decreases in lipohypertrophy from repeated use of the same site for injection, but its effect on blood glucose is limited (Overland et al. 2009). However, insulin absorption is strongly decreased in IDLA compared with lipohypertrophy (Gupta et al. 2015; Nagase et al. 2014; Kusuki et al. 2015; Yoshizaki and Honda, 2012). Therefore, the usefulness of identifying IDLA should not be overlooked because in these cases the dose of insulin can be significantly reduced by shifting the injection site.

In physical observation of IDLA at the insulin injection site, we often see changes in skin color, and the

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dermis is thickened and palpable as a nodular lump. However, physical findings such as subcutaneous lumps are not often observed in obese patients. For this reason, we investigated the detectability of subcutaneous lesions *via* ultrasound images at the insulin injection site and determined whether ultrasound could be used to detect cases in which subcutaneous lesions were not identified by physical observation.

Dermis and subcutaneous tissues can be clearly depicted with the use of high-frequency ultrasound probes (Valle and Zamorani 2007). Subcutaneous lumps caused by insulin injection, which can be identified by physical examination, can also be recognized by ultrasound (Perciun 2010; Perciun et al. 2012). However, there are no reports of ultrasound findings of subcutaneous lesions that are not palpable as lumps. Furthermore, there are no reports of a comparison between ultrasound findings and pathologic findings. There are few reports of ultrasound identification of subcutaneous lesions, especially IDLA, caused by insulin injection (Kusuki et al. 2015; Yoshizaki and Honda, 2012); their detailed characteristics remain unknown.

In preparation for future differential diagnosis of subcutaneous lesions at the insulin injection site by ultrasound, we aimed to elucidate the characteristics of ultrasound images of IDLA. Diagnosis of IDLA is confirmed by pathologic diagnosis after tissue biopsy. However, it is difficult to perform invasive biopsy on all patients suspected of having IDLA in routine practice because of patient consent and medical ethics issues. Therefore, if it can be diagnosed as IDLA by ultrasound, guidance to patients about shifting the injection site can be instantly provided, and additionally, a dosage adjustment for excessive insulin administration becomes possible. This may not only affect the treatment of diabetes, but may contribute to improving the patient's prognosis.

In this study, we histopathologically examined subcutaneous tissues of patients who were suspected of having IDLA clinically based on poor diabetes control, even with overdoses of insulin, and we prospectively examined ultrasound images of 22 histologically proven IDLA lesions. We quantitatively and qualitatively analyzed the ultrasound images of these cases, examined the feasibility of ultrasound diagnosis of IDLA and also discussed the association between IDLA and glycemic control. In other words, we investigated whether ultrasound of subcutaneous lesions found at the insulin injection site can compensate for physical examination for the identification of non-palpable lesions. In addition, we focused on elucidating the ultrasound characteristics of IDLA because it is necessary to detect and diagnose IDLA early to improve diabetes control. Furthermore, we investigated retrospectively whether shifting the injection site after detecting IDLA by ultrasound affected diabetic control for 22 patients.

METHODS

Insulin-induced subcutaneous lesions at the insulin injection site (abdominal wall) in 333 people with diabetes were physically and ultrasonically identified among 656 people undergoing insulin treatment from 2011 to 2014 (50.8%). Histopathological examination was performed in 26 patients with poor blood glucose control who consented to this study. Twenty-two of the 26 patients (84.6%) were diagnosed pathologically with IDLA and entered this study. Pathologic diagnosis of IDLA was performed by a pathologist using Congo red or direct fast scarlet stain and observation under a polarizing microscope (Fig. 1).

Definition of subcutaneous lesions and classification into two types

The decision to remove subcutaneous lesions was made by a diabetes care counselor after visual inspection and palpation and corroboration by the attending physician. Ultrasound observations were routinely performed after physical observation without knowledge of the findings. Patients were asked about the sites of insulin injection, and then an ultrasound scan was performed of the whole abdominal wall after checking each site; transverse and sagittal scan images were obtained by parallel scanning by B-mode. A site not injected was regarded as the intact region (Fig. 2), and the following were diagnosed as subcutaneous lesions by ultrasound (Fig. 3) compared with the intact region: (i) a thickened dermis (Fig. 3a), (ii) an unclear boundary between the dermis and the subcutaneous layer (Fig. 3b), (iii) differing echogenicity of the subcutaneous tissue (Fig. 3c–f), (iv) a recognized acoustic shadow in the subcutaneous tissue (Fig. 3f) and (v) absence of a fibrous septum in the subcutaneous tissue (Fig. 3c–f). Furthermore, after confirmation of the subcutaneous lesion with ultrasound, the registered medical sonographer palpated the site and confirmed whether the subcutaneous lesion was palpable or non-palpable. The ultrasound observations were performed by one registered medical sonographer. The ultrasound diagnosis of a subcutaneous lesion was ultimately judged by the attending physician.

Ultrasound equipment and settings

Insulin injection sites were observed with a high-frequency (13–14 MHz) linear probe (ML6-15, GE Healthcare, Wauwatosa, WI; 14 L-5, Toshiba Medical Systems, Tochigi, Japan) using ultrasound units (LOGIQ E9, GE Healthcare; Aplio400, Toshiba Medical Systems). The settings for both ultrasound devices were as