Insulin-induced Lipohypertrophy: Report of a Case with Histopathology

JUNJI FUJIKURA, MUNEYA FUJIMOTO, SHINTARO YASUE, MICHIO NOGUCHI, HIROAKI MASUZAKI,
KIMINORI HOSODA, TAKAO TACHIBANA*, HAJIME SUGIHARA** AND KAZUWA NAKAO

Department of Medicine and Clinical Science, Division of Endocrinology and Metabolism, Kyoto University Graduate School of Medicine, Kyoto 606-8507, Japan

**Department of Dermatology, Tenri Yoroze Hospital, Nara 632-8552, Japan*

***Department of Pathology, International University of Health and Welfare, Okawa 831-0004, Japan*

Abstract. An 82-year-old woman with type 2 diabetes had been treated with recombinant human insulin for 16 years. She developed large swellings in both sides of her lower abdomen. The masses were soft, painless, and located around her insulin injection sites. Based on the history and clinical features, a diagnosis of insulin-induced lipohypertrophy was made. Total resection revealed that the lesions were composed entirely of fatty tissue. Microscopic examination showed nests of mature adipocytes expanding toward the dermal reticular layer. The hypertrophic adipocytes were twice as large as those from normal subcutaneous areas and contained numerous small lipid droplets. Electron microscopic analysis also revealed a minor population of small adipocytes, suggesting active differentiation or proliferation. Thus, the possible *in vivo* effects of insulin on adipocytes were clearly observed in this case of insulin-induced lipohypertrophy. To our knowledge, this is the first report of insulin-induced lipohypertrophy with detailed histological examinations.

Key words: Insulin-induced lipohypertrophy, Adipocytes, Scanning electron microscopy

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THE incidence and prevalence of diabetes mellitus is increasing at an alarming rate [1]. Good glycemic control reduces the risk of complications of diabetes. Secondary failure of oral hypoglycemic treatment is common in patients with type 2 diabetes, and thus insulin treatment is often needed to improve glycemic control. Indeed, in the UK prospective diabetes study, with over 10 years of observation, 38% of patients needed insulin treatment to reduce fasting plasma glucose concentrations to <6 mmol/l [2]. Furthermore, modern therapy involves greater and earlier use of intensive insulin regimens to achieve better control of blood glucose levels and reduce the long-term risks of diabetes [3].

Insulin therapy is associated with skin related com-

plications, such as lipoatrophy, lipohypertrophy, edema, or allergy [4]. Among them, lipohypertrophy is the most common cutaneous complication, characterized by a tumor-like swelling of fatty tissue around subcutaneous insulin injection sites [5–7]. The purpose of this case report is to present a detailed histological analysis of insulin-induced lipohypertrophy in a patient with type 2 diabetes mellitus.

Case Report

An 82-year-old woman with type 2 diabetes had been treated with insulin for 16 years. Initially, she was treated by her private physician; however, in December 2003, her physician noted soft painless swellings on her abdomen and she was admitted to our hospital. On admission, she was 147 cm tall and weighed 46 kg (BMI 21.3 kg/m²). Her blood pressure was 121/68 mmHg and pulse rate was 66 beats per

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Correspondence to: Dr. Junji FUJIKURA, 54 Shogoin Kawaracho, Sakyo-ku, Kyoto, Kyoto 606-8507, Japan

minute. She was taking 6 units of regular insulin before meals and 6 units of NPH insulin at bedtime. Her diabetic control was poor (HbA1c 8.3%) and she displayed mild diabetic neuropathy. She had developed two large masses, one at each side of her lower abdomen (Fig. 1). Both masses were soft, rounded,

and movable, and were about 10 cm in diameter. There were scars on the surface of the skin, areas that represented her current insulin injection sites (arrows in Fig. 1). No other clinical abnormalities were present. Hematological and biochemical tests were unremarkable (Table 1). Based on the above

Fig. 1. Large movable abdominal masses. Pictures were taken in two body positions, standing (left) and spine (right). There are scars at the sites of insulin injections (arrows).

Fig. 2. Surgically resected specimen. Outside view (left) of the whole specimen and a cross-sectional view (right) of the specimen. The two masses were composed of yellowish fatty tissues and were not encapsulated by fibrous tissues.

Table 1. Laboratory data

White blood cell	6100/ μ l	γ -glutamyltranspeptidase	13 IU/l	HbA1c	
Red blood cell	434×10^4 / μ l	Total cholesterol	213 mg/dl	before surgery	8.3%
Hemoglobin	11.8 g/dl	High density lipoprotein	50 mg/dl	after surgery	7.1%
Hematocrit	37%	Triglyceride	60 mg/dl	Leptin	
Platelet	19.4×10^4 /ml	Blood urea nitrogen	21 mg/dl	before surgery	2.8 ng/ml
CRP	0.3 mg/dl	Creatinine	0.7 mg/dl	after surgery	4.6 ng/ml
Aspartate aminotransferase	25 IU/l	Uric acid	4.5 mg/dl	Adiponectin	
Alanine aminotransferase	15 IU/l	Fasting plasma glucose	8.3 mmol/l	before surgery	25.8 mg/ml
Lactate dehydrogenase	231 IU/l	GAD antibody	negative	after surgery	31.1 mg/ml
Alkaline phosphatase	218 IU/l	Anti-Insulin antibody	34.2%		

findings, a clinical diagnosis of insulin-induced lipohypertrophy was made. She was instructed to avoid the abdomen as a site for injections and to use a multi-rotation method. Her glycemic control improved after changing insulin injection sites. However, the hypertrophy was not resolved after a month. Surgical excision for cosmetic purposes was performed under local anesthesia. The en bloc-resected surgical specimen was $24.2 \times 9.9 \times 3.0$ cm, and weighed 405 g (Fig. 2). The lesions were composed entirely of a yellowish material and were not encapsulated by fibrous tissues. The gross findings were compatible with benign lipohypertrophy. Although the tumors were large, her serum leptin and adiponectin levels were not significantly changed after surgery (Table 1). Light and electron microscopic examinations were carried out on the lipohypertrophic tissues and surrounding normal adipose tissues. Hematoxylin and eosin (HE) staining

of sections from lipohypertrophic tissues showed excess mature adipocytes in the dermal reticular layer (Fig. 3A). We observed a significant increase in the size of adipocytes in the lipohypertrophic area (diameters 100 to 200 μ m, Fig. 3B), compared with the surrounding normal areas (diameters 70 to 90 μ m, Fig. 3C). This increase in the volume of adipocytes was confirmed with scanning electron microscopy (SEM) (Fig. 4). Approximately 10% of the adipocytes in the lipohypertrophic area contained numerous lipid droplets at their periphery, as seen by light microscopy (arrow in Fig. 5A) and SEM (Figs. 5B and 5C), showing stimulated lipogenesis. Some heterogeneity in the size of adipocytes was observed in the lipohypertrophic area (Figs. 4 and 6). A few adipocytes, surrounded by hypertrophic adipocytes, were as small as 20 μ m in diameter (arrowheads in Fig. 6).

Fig. 3. Fat infiltration in the dermis (A) and hypertrophic adipocytes (B). Hematoxylin-eosin (HE) stained sections from the insulin-induced lipohypertrophy (A, magnification: $\times 40$; B, magnification: $\times 200$) and the adjacent normal subcutaneous adipose tissue (C, magnification: $\times 200$).

Fig. 4. Hypertrophic adipocytes. Scanning electron microscopy of the insulin-induced lipohypertrophy (left) and adjacent normal subcutaneous adipose tissue (right) at magnifications of $\times 50$ (upper) and $\times 100$ (lower).

Discussion

Lipodystrophy is a potential clinical adverse effect associated with intensive insulin therapy.

Insulin-induced lipoatrophy is the loss of subcutaneous fat at the site of insulin injection. Although this complication occurred in 25%–55% of patients before the development of highly purified recombinant human insulin, it is now quite rare [8]. The pathological mechanisms therefore may have involved an immune-mediated inflammatory reaction to impurities in the insulin products [9].

The prevalence of insulin-induced lipohypertrophy is reported to be 29% in patients with type 1 diabetes and 4% in patients with type 2 diabetes [5]. Our patient preferentially injected at the same sites because of their relative anesthesia. The total dose of administered insulin was estimated to be as much as 103,800 units. Furthermore, she believed that all diabetics who used insulin inevitably had such swellings. Lipohyper-

trophic nodules have decreased vascularity, which delays insulin absorption [10]. Recent reports show that lipohypertrophy is a very frequent problem in diabetic patients associated with poor glycemic control [6, 11]. In this patient, there was good improvement in her glycemic control (HbA1c 7.1%) after changing insulin injection sites.

The pathophysiology of insulin-induced lipohypertrophy is generally thought to be the result of the lipogenic effects of insulin. Our histological examination clearly shows the consequences of the lipogenic actions of insulin on adipocytes (Figs. 3–5). However, although the enlarged adipocytes are impressive (Figs. 3 and 4), the large volume of lipohypertrophic mass is only partially explained by the levels of cellular hypertrophy. In human obesity, when body weight exceeds 170% of ideal, a maximum adipocyte size of the twice normal is achieved and hyperplasia becomes increasingly manifest with greater severity [12]. It is well known that insulin stimulates proliferation and dif-

Fig. 5. Numerous small lipid droplets at the periphery of hypertrophic adipocytes. HE staining (upper, magnification: $\times 400$) and SEM (lower left; magnification: $\times 500$; lower right, magnification: $\times 1500$) of the insulin-induced lipohypertrophy. The arrow in the upper picture shows subcellular lipid droplets. The lower SEM images show exposed lipid droplets underneath the plasma membrane.

ferentiation of preadipocytes [13, 14]. The possible asymmetric cell division of mature human adipocytes has also been reported [15, 16]. Small adipocytes seen in the lipohypertrophic area (arrowheads in Fig. 6) would be newly formed adipocytes, arising either by differentiation or by proliferation, in the course of maturation. Taken together, lipohypertrophy is therefore assumed to be the result of maximum hypertrophy and accompanying hyperplasia stimulated by insulin.

The treatment of insulin-induced lipohypertrophy is to change injection sites in the hope that regression will occur. However, when the excessive fat tissue does not decrease, an invasive surgical procedure is necessary. Further analyses of cases would reveal the pathological mechanisms of insulin-induced lipohypertrophy and provide theoretical foundations for prevention and less invasive treatments.

Fig. 6. Heterogeneous size of adipocytes in the insulin-induced lipohypertrophy. Arrowheads in the SEM (magnification: $\times 200$) image indicate small adipocytes.

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