Lipodystrophy is a disorder affecting subcutaneous fat and can result in lipoatrophy or lipohypertrophy. Before the advent of recombinant human insulin, insulin-induced lipoatrophy was a common problem among insulin users. Lipoatrophy is a clinical condition characterized by localized loss of subcutaneous fat. The prevalence of lipoatrophy was reported to be as high as 24–55% with animal insulins (1). Fortunately, with the use of human insulin, lipoatrophy has become a rare complication (2). Lipohypertrophy is characterized by increased localized adipose tissue mass. Its prevalence is reported to be as high as 20–30% in people with type 1 diabetes using human insulin products (3).

Lipodystrophy resulting from insulin use is localized to insulin injection sites, and its presence might affect insulin absorption. The pathophysiological mechanism of insulin-induced lipodystrophy remains to be determined. Although various mechanisms have been proposed, presence of high-titer anti-insulin antibodies and individual susceptibility to these conditions point toward an immune-mediated mechanism. Concurrent occurrence of lipoatrophy and lipohypertrophy in the same patient is uncommon and, to the best of our knowledge, has not been reported previously.

**Case 1 Presentation**
A 12-year-old girl with type 1 diabetes for the past 3 years presented with inadequate glycemic control and significant unexplained glycemic variability. She was taking human regular insulin three times per day before meals and human NPH insulin before breakfast and dinner. She had localized lipoatrophy on the abdomen (noted for the past 3 months). Her weight, height, and BMI were 26.3 kg, 130.2 cm, and 15.56 kg/m², respectively. On examination, she had a localized area of depression on the right side of the abdomen (lipoatrophy), as well as lipohypertrophy on the left side (Figure 1). Her A1C was 8.8%, and her anti-insulin antibody level was >100 U/mL (normal <10 U/mL). MRI of the affected part of the abdomen showed subtle lipoatrophic and lipohypertrophic changes. After changing the injec-
tion site, her blood glucose levels and
glycemic variability improved. After 3
months, her A1C was 7.6%.

Case 2 Presentation
An 8-year-old girl with type 1 dia-
betes for the past 2 years presented
to our clinic. She stated that she had
been suffering from recurrent epi-
sodes of unexplained hypoglycemia.
She was taking human regular insu-
lin twice daily and premixed human
insulin (regular 30/NPH 70) once
daily. Home capillary blood glucose
readings showed erratic and variable
glycemic control. There was no his-
tory suggestive of fever, infection,
foot ulcer, organ dysfunction, or en-
docrinopathy. On examination, her
weight, height, and BMI were 19.2
kg, 114.7 cm, and 14.41 kg/m², re-
spectively. There was localized loss of
fat (lipoatrophy) and lipohypertrophy
on the abdomen (Figure 2). Her A1C
was 10.4%, and her anti-insulin an-
tibody titer was >100 U/mL. MRI
of the affected part of the abdomen
showed significant loss of subcutane-
ous fat in one area and lipohypertro-
phy elsewhere (Figure 3). A punch
biopsy from the lipoatrophic area
showed absence of subcutaneous fat
and inflammatory cells (Figure 4).
We advised her to take insulin in
her unaffected thigh and also to ro-
tate her injection sites. Over the next
few weeks, her home blood glucose
readings improved significantly, with
far fewer episodes of hypoglycaemia.
After 3 months, her A1C had de-
creased to 9.6%, with improvement
in the lipodystrophy.

Questions
1. Can lipoatrophy and lipohyper-
trophy occur in same patient?
2. What are the possible underlying
mechanisms?
3. Do these conditions affect glyce-
mic status?

Commentary
The pathogenesis of insulin-induced
lipodystrophy remains obscure. Among various proposed mecha-
nisms, immune complex–mediated
tissue damage is the most important.
It has been previously reported that
there is infiltration of inflammatory
cells, presence of antigen-antibody
complex, and deposition of immu-
noglobulin M with complement
component 3 or fibrin-fibrinogen
in the walls of dermal blood vessels
in affected areas (1). There is also in-
creased local production of inflamma-
tory cytokines such as tumor necrosis
factor α and interleukin-6 by T cells
and monocytes. De-differentiation of
adipocytes in the subcutaneous tissue
occurs, resulting in lipodystrophy (4).
Improvement of lipoatrophy with
local dexamethasone injection fur-
ther substantiates this hypothesis
(5). Some investigators have reported
that lipoatrophic areas are infiltrated
by an increased number of mast cells.
Degranulation of mast cells mediates
the local inflammatory process. Mast
cell stabilizer cromolyn sodium, when
given topically, resulted in significant
improvement (2).

Lipohypertrophy may be the result
of local anabolic action of insulin on
adipocytes, promoting fat and protein
synthesis. However, other mechanisms
such as reuse of needles and trauma
from frequent injections at the same
site have also been postulated (6).

Anti-insulin antibodies have an
important role in insulin pharma-
cokinetcis and immune-mediated
adverse effects such as lipodystrophy.
Antibody production is influenced
by several factors such as genetics,
degree of purity of the insulin, spe-
cies of insulin origin, and mode of
insulin administration. The antibod-
ies are usually of immunoglobulin
G– or immunoglobulin E– class
antibodies. Although animal insu-
lin has been associated with higher
titers of antibody production, it has
been observed that highly purified
human recombinant insulin can also
produce anti-insulin antibodies. It is
hypothesized that lipoatrophy is the
result of antigen antibody complex
formation (7). It is also important
to note that anti-insulin antibody
levels are positively correlated with lipohypertrophy (8).

Apart from related cosmetic concerns, the importance of insulin-induced lipodystrophy lies in alteration of insulin absorption and glycemic variability. Abnormal absorption kinetics from dystrophic areas produce erratic blood glucose levels, leading to unpredictable hypo- and hyperglycemia. Evidence suggests that clearance of insulin from lipohypertrophic areas is significantly delayed (9).

Specific treatment of lipohypertrophy and lipoatrophy is still unavailable. As described above, dexamethasone and cromolyn sodium have been tried in a few patients with variable results. Liposuction has been tried in lipohypertrophy (6). Although a specific susceptibility to insulin-induced lipodystrophy has yet to be uncovered, proper insulin administration technique and rotation of injection sites would be a prudent option to decrease the chances of these complications.

Both of the patients described here had lipoatrophy and lipohypertrophy in different injection sites. After ensuring proper injection technique, including rotation of sites, both had improvement in A1C and glycemic variability. We could not explain the mechanism behind the occurrence of both lipoatrophy and lipohypertrophy in the same patient. However, high-titer anti-insulin antibodies may be responsible. The presence of both lipoatrophy and lipohypertrophy in the same patient using recombinant human insulin is extremely rare and, to the best of our knowledge, has not been reported previously.

Clinical Pearls
• Insulin injection sites should be examined in every patient, particularly those who have variable glycemic status.
• Proper injection technique and rotation method should be advised to every patient taking insulin.

Duality of Interest
No potential conflicts of interest relevant to this article were reported.

References