Insulin induced lipodystrophy

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Abstract
Insulin induced lipoatrophy and, more commonly, lipohypertrophy are dermatological complications of insulin therapy. Lipoatrophy is becoming less common with the advent of newer insulin analogues; however, lipohypertrophy is still prevalent. Whilst an immunological mechanism is postulated for lipoatrophy, direct local anabolic action of insulin is postulated for lipohypertrophy. Other factors which are implicated are the duration of diabetes, the number of insulin injections, re-use of needles and pen devices. The best current preventative and therapeutic strategies for insulin induced lipohypertrophy include rotation of injection sites with each injection and non-reuse of needles. Topical dexamethasone injections have been tried for the management of insulin induced lipoatrophy. It is important that these complications are recognised and managed appropriately. Insulin absorption from these sites is unpredictable and can lead to erratic glycaemic levels and unpredictable hypoglycaemic attacks. This article raises awareness of the possibility of insulin induced lipodystrophy as a cause of poor glycaemic control.

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Introduction
Lipodystrophies are a heterogeneous group of disorders characterised by abnormal distribution of body fat which can be genetic or acquired and also can have a generalised distribution or a more localised (partial) distribution. Insulin induced lipodystrophy is an acquired partial lipodystrophy. Lipohypertrophy and lipoatrophy are two main inter-related but distinct dermatological complications of subcutaneous insulin injections. Of these, lipohypertrophy is a much more common complication than lipoatrophy. The prevalence of insulin induced lipohypertrophy is approximately 25-30% in patients with type 1 diabetes and <5% in patients with type 2 diabetes with subcutaneous insulin treatment. On the other hand, insulin induced lipoatrophy, though very rare, still continues to be reported. Since the introduction of insulin analogues, the incidence of lipoatrophy has fallen in recent years from 25-55% with treatment with non-purified bovine or porcine insulin preparations to around 3.6% with treatment with recombinant human insulin and analogues.

Diagnosis
Clinical findings
Lipohypertrophic areas usually present as soft dermal nodules like lipomas or fibrocollagenous scar tissue within the skin and can vary in size from golf balls to an orange (Figure 1). When large areas are involved, the appearance can be unsightly. Initial skin changes can be subtle and manifest only as thickening of skin. This can be easily missed by visual inspection and so areas should be palpated. It is recommended that, in order to feel subtle skin thickening, the hand should be stroked firmly in a sweeping motion rather than using traditional techniques of light and deep palpation. Most common areas involved are on either side of the umbilicus and mid thigh as these are commonly used sites for injection and are easily reached and convenient for patients. Lipodystrophic areas, on the other hand, present as localised areas of fat loss and can be cosmetically unsightly (Figure 2).

Causes
Lipohypertrophy is thought to be the direct anabolic effect of insulin on local skin leading to fat and protein synthesis and hence this is observed even with recombinant insulin preparations and continuous insulin infusion pumps. This complication occurs because of repeated injections at the same site. As these areas are relatively painless, patients tend to inject in the same area again and again rather than move to a new painful site. Other possible risk factors associated are type 1 diabetes due to longer duration of insulin therapy, high number of insulin injections, re-use of needles and pen devices.
injections, reuse of needles with a significant increase if used more than five times and use of pen devices. Development of insulin antibodies is also suggested as a possible underlying mechanism.\textsuperscript{10,11}

Lipoatrophy is considered an immune mediated inflammatory response. Although it was much commoner with bovine and porcine insulin, it still remains a complication of insulin therapy irrespective of the insulin source (animal, recombinant, or analogue) and the mode of administration.\textsuperscript{12,13} The respective exposition to the analogues lispro, aspart, glargine and detemir prior to lipoatrophy development varies between 4 weeks and 2 years.\textsuperscript{14} Lipoatrophy can also occur with CSII therapy\textsuperscript{15} and more than one type of insulin analogue in the same patient.\textsuperscript{16}

Repeated use of the same insulin injection site and multiple usage of the same pen needle increases the risk of lipoatrophy.\textsuperscript{12}

Atrophy results from the local formation of complexes between injected antigen and circulating antibody with activation of complement and infiltration of inflammatory cells. This is similar to the classical Arthus immunological reaction where atrophy happens because of local deposition of immune complexes formed from injected antigen and circulating antibodies followed by an acute vasculitis. Local overproduction of cytokines and tumour necrosis factor from mast cells may inhibit adipocyte differentiation. Anti-insulin antibodies were thought to be strongly associated with the development of skin atrophy.\textsuperscript{10}

Although patients may describe transient red nodules or urticarial lesions soon after commencing insulin injections, the clinical appearance of lipoatrophy is notable for its lack of inflammatory features. This contrast with the Arthus reaction is probably due to the considerable difference in antigenicity between whole horse serum used in the classical Arthus experiments and re-crystallised insulin preparations and to different dose and frequency of injections.\textsuperscript{10}

**Histopathology**

Histology from lipohypertrophic areas show an increase in the size of fat cells, nearly double the volume compared with the fat cells from surrounding normal skin. Discrete areas of small adipocytes at the periphery possibly represent proliferation.\textsuperscript{17} The appearance of collagenous scar tissue with hypovascular collagen and bland looking fibroblasts has also been described.\textsuperscript{7}

Histology from lipoatrophic areas show degenerative changes in adipose tissue with deposition of IgM, complement\textsuperscript{3} or fibrin-fibrinogen in dermal blood vessels at the edges of these sites.\textsuperscript{18} This suggests an immune mechanism, further supported by the finding of a much higher insulin-binding capacity in patients with lipoatrophy.\textsuperscript{10}

**Management**

It is important that these complications are recognised and managed appropriately. Insulin absorption from these sites is unpredictable and can lead to erratic glycaemic levels and unpredictable hypoglycaemic attacks.\textsuperscript{2,12} When large areas are involved, it can be cosmetically unsightly and socially embarrassing for patients.

Injection sites should be examined at least annually by a health care professional for possible lipohypertrophy or lipoatrophy. Individuals should also be taught to examine their own injection sites and how to detect lipohypertrophy.\textsuperscript{5,19} Individuals should be advised not to inject into areas of lipohypertrophy until abnormal tissue returns to normal, which will take several months or even years. Switching injections from areas of lipohypertrophy to normal tissue often requires a decrease in the dose of insulin injected. The amount of change varies from one individual to another and should be guided by frequent blood glucose measurements. The best current preventative and therapeutic strategies for lipohypertrophy include rotation of injection sites and rotation of insulin injection devices.
sites with each injection and non-reuse of needles.\textsuperscript{19}
Changing injection sites helps in preventing development of lipohypertrophy. Patients should be educated regarding proper injection techniques and rotating injection sites. Patients should be taught self examination for early recognition of skin changes and to avoid these areas. Clinicians should examine the skin annually as advised by Diabetes UK. Changing insulin to rapid acting humanised insulin has been shown to decrease this side effect as adipocytes are in contact with insulin for short periods and thus local lipogenic effects are minimised.\textsuperscript{20} If conservative steps fail, then liposuction is an effective alternative.

Changing or rotating the site of insulin injection and changing type of insulin were traditional approaches to prevent further lipohypertrophy. Switching to CSII\textsuperscript{12} and/or short acting insulin analogues are alternative methods. These lesions can sometimes spontaneously regress, but use of small amounts of dexamethasone along with insulin injections was found to be beneficial.\textsuperscript{21} Injection of dexamethasone into the lipoatrophic lesions resulted in spontaneous regression, but use of small amounts of dexamethasone analogues are alternative methods. These lesions can sometimes spontaneously regress, but use of small amounts of dexamethasone along with insulin injections was found to be beneficial.\textsuperscript{21} Injection of dexamethasone into the lipoatrophic lesions resulted in return of subcutaneous fat tissue in a few cases.\textsuperscript{22,23}

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\textbf{References}