REVIEWS

The Cutaneous Adverse Events at the Site of Insulin Injections

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Abstract

Cutaneous adverse events at the site of insulin injections include local allergic reactions to insulin (erythema, pruritus, and induration) and lipodystrophy. Clinical forms of lipodystrophy include lipoatrophy and lipohypertrophy. Currently lipohypertrophy is the most common cutaneous complication of insulin therapy. Lipodystrophy is not reversible and the best treatment for this complication is prevention (routinely rotate the injection sites). Lipoatrophy treatment involves the use of glucocorticoids and cromolyn. Lipohypertrophy treatment involves conservative treatments and liposuction in the severe cases. Lipodystrophy is a common complication associated with insulin therapy, complication that can generate changes in insulin absorption and unpredictability of treatment.

Keywords: diabetes, insulin therapy, lipodystrophies

Rezumat

Reacțiile adverse cutanate la nivelul zonelor de administrare ale insulinei includ reacții alergice locale (eritem, prurit și indurare) și lipodistrofie. Formele clinice de lipodistrofie sunt reprezentate de lipoatrofie și lipohipertrofie. În prezent, lipohipertrofia este cea mai frecventă complicație cutanată a terapiei cu insulină. Lipodistrofia nu este reversibilă și cel mai adecvat tratament pentru această complicație este prevenția (ritmicitatea locurilor de injectare). Tratamentul lipoatrofiei implică utilizarea de glucocorticoizi și acid cromoglicic. Tratamentul lipohipertrofiei implică tratamente conservatoare și eventual liposucție în cazurile severe. Lipodistrofia este o complicație frecventă asociată cu terapiei cu insulină, complicație care poate genera modificări în absorbția insulinei și imprevizibilitatea tratamentului.

Cuvinte cheie: diabet zaharat, insulinoterapie lipodistrofie

INTRODUCTION

Cutaneous adverse events at the site of insulin injections include local allergic reactions to insulin (erythema, pruritus, and induration) and lipodystrophy The allergic reactions are usually short-lived, and resolve spontaneously within a few weeks[1]. Lipodystrophies are a group of diseases characterised by a morphological and/or functional impairment of the adipose tissue. Classification of lipodystrophy include genetic and acquired forms. Acquired forms can be generalized (Lawrence syndrome), partial (Barraguer-Simons syndrom, associated with sclerodermia or acquired immunodeficiency syndrome and antiretroviral therapy), or local (associated with drug: glucocorticoids, post-injection-insulin, somatostatin analogs, pegvisomant)[2]. Clinical forms of lipodystrophy include lipoatrophy and lipohypertrophy. In an issue of the *American Journal of Clinical Dermatology* published in 2003 entitled „*Skin-related complications of insulin therapy: epidemiology and emerging management strategies*", Richarson T and Kerr D assert that „*Common complications of subcutaneous insulin injection include lipoatrophy*

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and lipohypertrophy. The development of lipoatrophy may have an immunological basis, predisposed by lipolytic components of certain insulins. Lipohypertrophy is the most common cutaneous complication of insulin therapy"[1].

GENERAL CONSIDERATIONS

Lipoatrophy is defined by the loss of subcutaneous fat at the site of insulin injection. The pathogenesis of insulin-induced lipoatrophy is still unknown. Many theories suggest that lipoatrophy secondary insulin therapy appears to be an immune complex-mediated inflammatory lesion[3,4]. In an issue of the Diabetes Care published in 1996 entitled „*Insulin-Induced Lipoatrophy in Type I Diabetes: a possible tumor necrosis factor-α-mediated dedifferentiation of adipocytes*", Gepner CA and coworkers report that „*local hyperproduction of TNF-α from macrophages that was induced by the injected insulin could explain the dedifferentiation of the adipocytes of the subcutaneous tissue*"[5]. The incidence of lipoatrophy in patients using animal-derived insulins ranged from 10 to 55%[6] and significantly reduced with modern insulins. Lipoatrophy continues to be reported with insulin analogs[7,8]. Lipoatrophy can generate unpredictable absorbtion of insulin (absorption of insulin might be more rapid comparison to normal skin).

Lipohypertrophy is characterized by a tumor-like swelling of the fatty tissue around subcutaneous insulin injection sites. In different studies the prevalence of lipohypertrophy ranges from 27 to 49% in type 1 diabetes and 4% in type 2 diabetes) in different studies[9-12]. The pathogenesis of insulin-induced lipohypertrophy involved cellular response of adipocytes to the local effects of injected insulin and immunological factors. In case of lipohypertrophy the rate of insulin absorption is reduced. The appearance of lipohypertrophy in a man treated with basal bolus insulin therapy are presented is shown in Figure 1, and 2.

TREATMENT

Lipodystrophy is not reversible and the best treatment for this complication is prevention (routinely rotate the injection sites). In an issue of the *Diabetes & Metabolism*

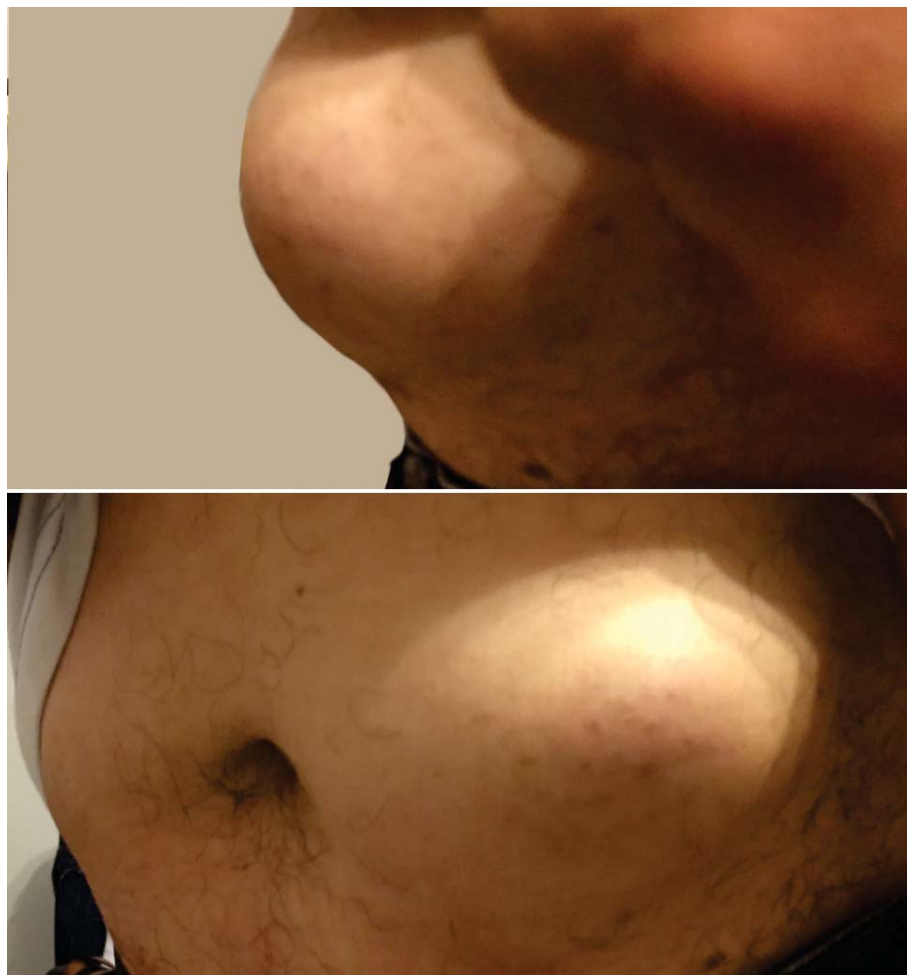

Figure 1, 2. Lipohypertrophy profile and front image in a mean treated with basal bolus insulin therapy.

published in 2013 entitled „*Prevalence and risk factors of lipohypertrophy in insulin-injecting patients with diabetes*", Blanco M, et al. report that „*injection site rotation appears to be the critical factor in preventing, lipohypertrophy which is associated with reduced glucose variability, hypoglycaemia, insulin consumption and costs*"[13].

Lipoatrophy treatment involves the use of glucocorticoids and cromolyn. Glucocorticoids have been used in the treatment of lipoatrophy because of their immunomodulating properties and their ability to produce a differentiation of adipocytes[5,14]. Phua EJ, et al., demonstrated previously „*increased degranulating tryptase/chymase-positive mast cells in biopsies from insulin-induced lipoatrophic sites and reported that topical cromolyn sodium (prepared with 4% cromolyn sodium in petrolatum solvent for topical administration twice daily to affected areas) was efficacious therapy in a small series*"[15]. Cromolyn is a mast cell stabilizer, inhibiting the release of of mediators that would attract inflammatory cells[16].

Lipohypertrophy treatment involves conservative treatments and liposuction in the severe cases[17].

Lipodystrophy may reduce circulating levels of hormones secreted by the adipose tissue. Given this fact was taken into account therapeutic agents that may increase circulating levels of adipokines or the use of adipokines (peroxisome proliferator-activated receptor γ agonists growth hormone and growth-hormone-releasing factors, recombinant analog of leptin)[18]. The *Food and Drug Administration* has approved in 2014 the leptin analog (metreleptin) in the treatment of generalized lipodystrophy in the adult and pediatric population but not in metabolic disorders associated with partial lipodystrophy[19].

CONCLUSIONS

Lipodystrophy is a common complication associated with insulin therapy, complication that can generate changes in insulin absorption and unpredictability of treatment.

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