Human Insulin Analog–Induced Lipoatrophy

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OBJECTIVE — To characterize the pathophysiology of recombinant human insulin-induced lipoatrophy.

RESEARCH DESIGN AND METHODS — We performed immunologic laboratory evaluation and skin testing for different insulin analogs and diluents in patients with type 1 diabetes and severe insulin-induced local lipoatrophy. Subcutaneous adipose tissue biopsies of areas of acute (7 days) and chronic insulin administration were examined. Topical sodium cromolyn was applied twice a day to atrophic areas and prophylactically to new sites of insulin administration.

RESULTS — Subcutaneous adipose biopsies showed an elevated population of tryptase-positive, chymase-positive degranulated mast cells. Of five patients treated with topical sodium cromolyn, none had new lipoatrophic sites and four showed improvements in old lesions.

CONCLUSIONS — Tryptase-positive/chymase-postitive mast cells, known to be sensitive to sodium cromolyn, may contribute to the destructive immune process mediated in response to exogenous insulin. Mast cell stabilizing therapy with topical cromolyn may reverse early and prevent new lipoatrophic lesions.

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RESEARCH DESIGN AND METHODS

— Five patients with severe local insulin-induced lipoatrophy were evaluated via blood tests performed at Quest Diagnostics for human insulin IgE and IgG, latex IgE, serum protein electrophoresis, erythrocyte sedimentation rate, antinuclear antigen, rheumatoid factor, tryptase, tumor necrosis factor-α, and complement levels C3, C4, CH50. Percutaneous testing (prick) was performed with multiple insulin analogs (regular, NPH, lispro, aspart, glulisine, glargine, and detemir) at 1:1,000, 1:100, and 1:10 dilutions and undiluted (100 units/ml). Histamine (20 mg/ml) was used as positive control, and diluent of each preparation was used as negative control. Subcutaneous fat biopsies of unaffected sites and areas of acute (7 days) and chronic insulin administration were performed. Hematoxylin and eosin staining; direct immunofluorescence for IgG, IgA, IgM, C3, and fibrin; and mast cell staining with chymase, chloracetate esterase, c-kit, and tryptase were performed.

Topical 4% sodium cromolyn was prepared in petrolatum solvent, applied twice daily to atrophic areas, and applied prophylactically to new sites of insulin administration. Patient consent for photography was obtained.

RESULTS

— Three women and two men with severe local atrophy for 4.8 ± 4.4 years were evaluated (Fig. 1*A–C*). Lipoatrophy developed at age 16.2 ± 8.6 years after insulin administration for 10.4 ± 8.4 years. Lipoatrophy was associated with continuous insulin infusion in three of the subjects. Insulin analogs associated with lipoatrophy included aspart ($n = 4$), lispro ($n = 4$), NPH ($n = 3$), glargine ($n = 1$), and regular ($n = 1$). Lipoatrophy was seen with more than one type of insulin analog in three subjects; two subjects had previous exposure to animal insulins.

All blood laboratory tests were normal except for modestly elevated human insulin IgG antibodies in all patients (11–141 μg/ml [normal <9]) and marked elevation (6,036 μg/ml) in one. Only one case subject had positive skin tests, reacting to regular, NPH, lispro, aspart, and glulisine and detemir insulin types that the patient had not previously received.

Subcutaneous biopsies were available in four patients; one had insufficient tissue for evaluation. Subcutaneous tissue from acute and chronic injection sites showed various degrees of atrophy of lobular adipose tissue and variable extent of angiocentric and lobular lymphocytic infiltrate; eosinophils were prominent in three cases (Fig. 1*E–F*). Focal fibrosis was present in all chronic injection sites.

Increased numbers of interstitial and perivascular mast cells with active degranulation were demonstrated in both acute and chronic areas of insulin administration in all cases (Fig. 1*G–H*). Mast cells stained positively with tryptase and chymase antibodies and with c-kit and chloracetate esterase. Direct immunofluorescence for IgG, IgA, IgM, C3, and fibrin was negative. Clinically unaffected subcutaneous tissue showed only scattered mast cells without degranulation.

All five patients received topical cromolyn. After an average of 12 weeks (range 4–20), none of the patients developed additional lipoatrophic lesions at new injection sites. Four patients had significant improvement of lipoatrophy, with complete resolution in one patient after only 4 weeks of cromolyn (Fig. 1*C–D*). In this patient, aspart was first changed to lispro without noticeable improvement over 2 months; then, cromolyn was initiated. Of note, duration of lipoatrophy before intervention was shortest in this patient (4 months). Another patient had changed from aspart to regular/dexamethasone insulin mix (both via pump), with no improvement over 8 months but subsequent improvement following cromolyn. Additionally, one patient with glargine-induced lipoatrophy was switched to lispro via pump simultaneous to initiation of cromolyn; consequently, the effect of each cannot be distinguished.

The only patient without lipoatrophy improvement showed progression of lesions. Importantly, she had the longest time interval from initial ap-

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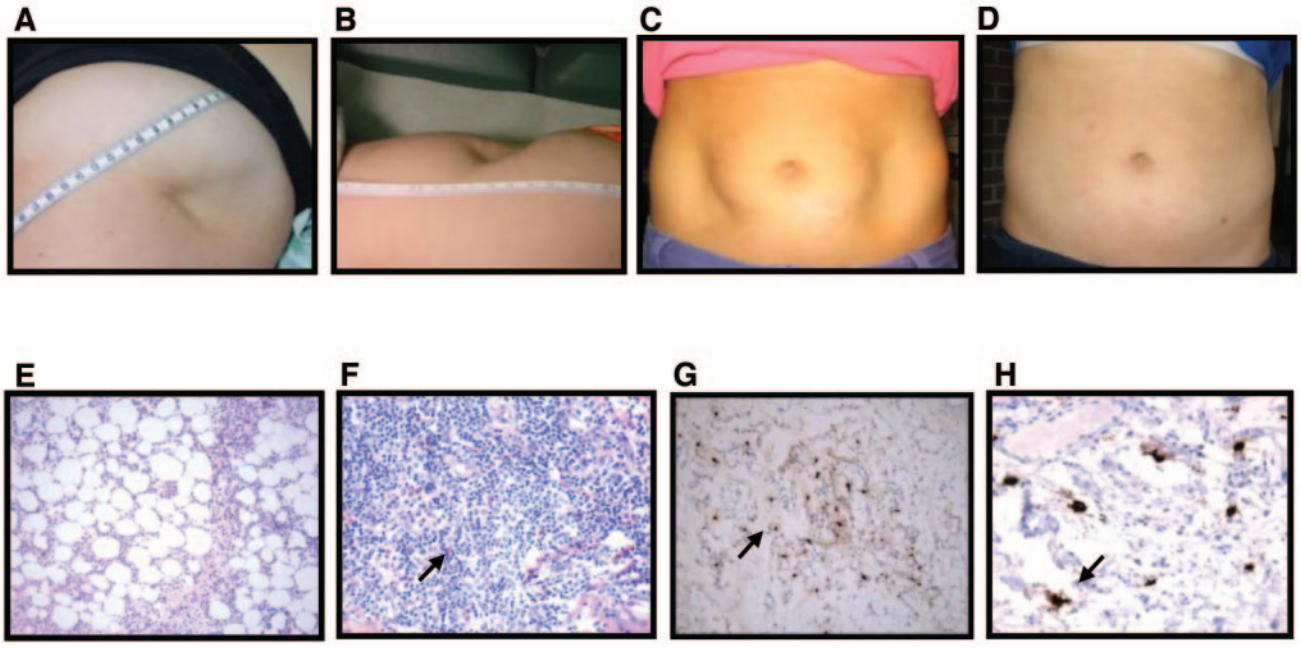

Figure 1—A–C*: Severe lipoatrophy lesions. Improvement of lipoatrophy before* (C) *and after* (D) *4 weeks of therapy with topical cromolyn. Acute injection site with marked lobular lymphocytic infiltrate* (E) *and numerous eosinophils* (F) *under hematoxylin and eosin staining. Increased mast cell population with degranulation under tryptase* (G) *and chymase* (H) *staining.*

pearance of lipoatrophy (12 years). This patient was also started on lispro/dexamethasone mix injections after 3 months of cromolyn therapy, and, likewise, no improvement was seen. All but this patient planned on continuing cromolyn therapy indefinitely.

CONCLUSIONS — We demonstrate increased numbers of degranulating mast cells in biopsies of insulin-associated lipoatrophy. In addition, three of four case subjects showed prominent eosinophils consistent with an allergy-mediated immune response. Mast cells were tryptase positive/chymase positive and known to be sensitive to sodium cromolyn and resistant to glucocorticosteroids, as opposed to tryptase positive/chymase negative, which are more resistant to cromolyn but respond to glucocorticosteroids (1).

Dexamethasone/insulin-mix therapy, in our experience, has variable and limited benefits, as does changing between different insulin preparations, suggesting cross-reactivity. Thus, we initiated therapy with topical sodium cromolyn. Cromolyn is a mast cell stabilizer, inhibiting the release of histamine in the presence of antigen-IgE antibody reactions probably via indirect blockade of extracellular calcium influx (2). It is highly polar and lipophobic and thus poorly absorbed through body surfaces; however, when compounded for topical use in emollient vehicles, it has been effective in the treatment of atopic dermatitis (3–6).

To our knowledge, this is the first time topical cromolyn has been used for local insulin-induced lipoatrophy. Interpretation of our findings is limited by the absence of control biopsies of insulin injection sites in individuals without lipoatrophy, the small number of patients, and the dual interventions in three of five patients. Nevertheless, no patient developed new lesions and four out of five patients showed improvement or resolution, suggesting that suppression of mast cell degranulation by cromolyn may also revert the inflammatory process via inhibition of additional mast cell recruitment. The patient with the longest clinical course did not show improvement of old lesions, suggesting that chronicity may limit the therapeutic potential of cromolyn.

Based on our findings, we hypothesize that mast cells found abundantly in areas of local insulin-induced lipoatrophy contribute pathologically to the destructive inflammatory process. These were tryptase-positive/chymase-positive mast cells, a subtype known to be sensitive to cromolyn but resistant to glucocorticosteroids (1). Therefore, lipoatrophic lesions may be expected to respond better to cromolyn than to glucocorticosteroid treatment. Furthermore, our findings suggest that therapy with cromolyn may reverse early and prevent new lipoatrophic lesions.

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