Investigations of Fat Grafting as a Treatment Modality for Skin Fibrosis in Scleroderma

Schmucker RW, Thayer JA, Butt FE, Gross J, Harrison C, Gupta A, Neumeister MW.

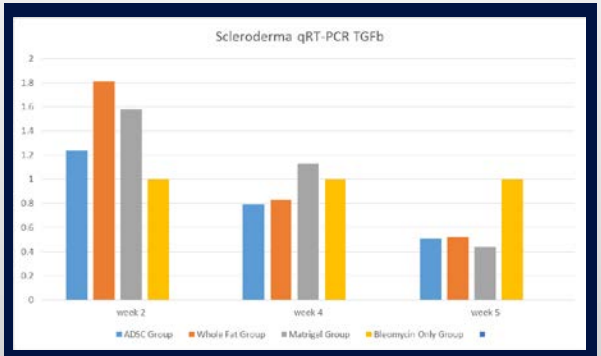
Southern Illinois University, School of Medicine, Springfield, IL

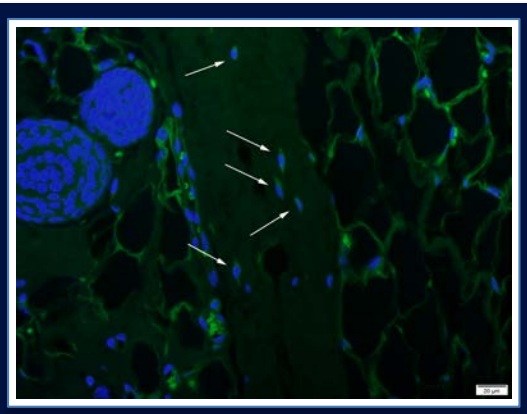
Introduction

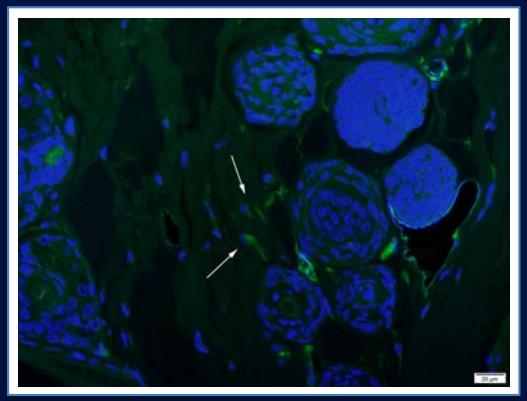
Scleroderma is a systemic autoimmune fibroproliferative disorder characterized by diffuse or localized fibrosis. Cutaneous manifestations such as sclerodactyly, joint contractures, and digital ulceration are a significant source of morbidity for the scleroderma patient and impair their activities of daily living. The purpose of this project is to evaluate fat grafting and adipose-derived stem cell (ADSC) injection as a treatment modality that induces regenerative skin changes in scleroderma using the bleomycin murine model. We hypothesize that fat grafting and ADSC injection in the setting of scleroderma will ameliorate fibrosis and rejuvenate the overlying skin. This could have major treatment implications related to the treatment of symptomatic sclerodactyly and digital ulcers.

Methods

Utilizing the bleomycin-induced scleroderma murine model, 56 adult nu/nu mice were divided into 4 groups with 15 mice each in the fat grafting, ADSC, and sham graft groups and 6 mice in the bleomycin only control group. All mice received daily subcutaneous injections of Bleomycin in the right parascapular area for 28 consecutive days. On day 28 the mice were injected in the right parascapular area with either fat graft (from GFP mice), ADSCs suspended in Matrigel, or Matrigel only (sham graft). 5 mice from each group were euthanized at 14, 28, and 35 days and skin was analyzed with laser doppler, dermal thickness and Type I collagen content. Scleroderma-relevant cytokines TGFb, endothelin-I, and angiotensin-II will be measured by qPCR. Immunohistochemical analysis will be performed to identify migration of engrafted fat and ADSCs in the dermis and epidermis.







Results

There was significantly less type I collagen formation in the ADSC group as compared to the sham and fat graft groups at the 2 week time point. Histologic data from weeks 4 and 5 is pending, but we expect to show the same significant improvements in these groups. On PCR analysis we found the expression of TGF-β and Endothelin-1 was lower at weeks 4 and 5 in the ADSC and whole fat groups compared to the bleomycin only control group. In addition immunohistochemical analysis showed migration of tagged ADSC cells into the basal layer of the dermis as early as week two, and further progression of viable cells into the superficial dermis by week 5.

Conclusion

The ADSC group demonstrated a statistically significant reduction in type I collagen formation as early as 2 weeks out following injection. ADSC and whole fat groups also showed a reduction in scleroderma-associated cytokines TGF-β and Endothelin-1 by weeks 4 and 5 compared to control. The migration of viable ADSCs from the site of grafting into the dermis as early as week two points toward a mechanism of rejuvenation of skin and amelioration of fibrosis when fat grafting is used in the setting of scleroderma.

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