Adipose-Derived Therapeutic Products for the Management of Refractory Crohn's Fistula

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Dear Editors:

We have read with great interest the recent article of Dige et al[1] published in *Gastroenterology* titled "Efficacy of injection of freshly collected autologous adipose tissue into perianal fistulas in patients with Crohn's disease." We would like to congratulate the authors of this article, who have performed a prospective interventional study reaching a rate of 57% of patients (12/21) with complete fistula healing 6 months after the last autologous adipose tissue injection. This study adds to a series of clinical studies over the last 15 years demonstrating the potential benefit of adipose derived products in refractory Crohn's fistula management.

We believe that some points merit discussion. First, we were surprised by the low rate (43%) of patients who achieved complete fistula healing after a single injection of adipose tissue. In comparison, darvadstrocel (Alofisel) and physiologic serum, respectively, reached 56.3% and 38.6% of combined remission (clinical and radiological assessments) 1 year after a single injection, whereas Dietz et al using autologous adipose-derived stem cells (ADSCs) applied in a bioabsorbable matrix observed 83% of complete clinical healing at 6 months.[2,3] In our own study, we also described a 60% combined remission rate at one year using a single co-injection of a microfat-enriched stromal vascular fraction (SVF).[4] One of the authors' hypothesis to explain these differences is the use of more stringent criteria in their study to define a healed fistula. Indeed, a fistula was considered completely clinically healed (i) if the patient had no symptoms of discharge, (ii) if there was no visible external fistula opening in the perineum, and (iii) if no internal opening could be palpated with rectal digital examination. In the absence of consensus, the only common criteria allowing comparison of these clinical trials 6 months after a single procedure is "cessation of drainage of external openings despite a gentle finger compression." Moreover, drainage was already used as healing fistula criteria in the pivotal clinical trial of infliximab for the treatment of fistulas in patients with Crohn's disease.[5] Thus, the healing fistula rate range from 48% to 83% with fat alone and ADSCs applied in a bioabsorbable matrix, respectively. The only randomized controlled study describes intermediate results of 55% and 43% of healing fistula rates with allogenic ADSCs and physiologic saline. This finding emphasizes the need for a consensus definition of fistula healing and to what extent it should include radiological assessment.

Second, adipose tissue grafting is a complex field and a large variety of harvesting and manufacturing methods exist. Dige et al described a standard harvesting with 3.5-mm liposuction cannula, a centrifugation step and a final shifting of adipose tissue between 10-mL syringes allowing. Details should be mentioned regarding the shifting step, particularly the number of passes and the diameter of the connector. From our point of view, this could correspond to the "nanofat" described by Tonnard in 2013 where 30 passes are sufficient to emulsify the fat and obtain a liquid product. In this case, the adipose tissue structure is completely disturbed and replaced by an oily emulsion containing regenerative cells without viable adipocytes, with a limited filling capacity.[6] The authors describe an excellent viability and composition of SVF within adipose tissue, showing that their manufacturing process did not impair it. However, it could have been interesting to evaluate the impact of this process on adipocytes' integrity. We prefer to use dedicated harvesting device to obtain smaller lobules of adipose tissue ($\sim$ 600 μm) without shifting step, also called "microfat," which may have greater trophic and regenerative qualities than adipose tissue harvested according to "standard" technique.[7] Also, we have decided to use a purification step of microfat through filtration, described as preserving tissue viability with less contaminants, rather than centrifugation.[8]

In conclusion, fat autograft and SVF injection are emerging as promising strategies for Crohn's fistula healing. Future controlled and comparative studies are now expected to establish efficacy using standardized endpoints.

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