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Lipogems: A New Device in Regenerative Medicine Providing a Natural Living Implantable Bioreactor. A Short Review [Version 1, 1 Approved with Reservations]

Carlo Tremolada* and Silvia Versari

Image Institute, Italy

*Corresponding author: Carlo Tremolada, Image In stitute, Milan, Italy, Email: carlo.tremolada@gmail.com

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Abstract

ALipogems® is a novel and easy system designed to harvest, process and inject a refined aspirated fat tis-sue characterized by a great regenerative potential and optimal surgical handling.By the aid of this technology, the fat tissue is washed, emulsified and rinsed, while cluster dimensions are gradually re-duced in a completely closed device - the Lipogems® device- by only mechanical forces.

Lipogems® tissue product represents a natural implantable bioreactor thatincorporates the main elements for a perfect natural regenerative response: the Scaffold (the adipose tissue structure), the Cells (Pericytes/MSCs), and the Grow factors (secreted cytokinesand chemokines).

The local injection of such a tissue that can work for long time enhancing the natural healing potential, may explain way its clinical use have been so successful in many fields with, apparently, no drawbacks.

The purpose of this short review is to present the concepts and experience with theLipogems® technol-ogy and to clarify the role that this new approach has acquired in regenerative medicine and surgery so far.

Fat Tissue Potential: An Ideal MSCs Source

The concept that fat tissue is an optimal source for MSCs (ASCs) is now well established [1-5], mostly be-cause of their abundance compared to other tissues [4-8]. Indeed, 1/100 cells in the adipose tissue is anASC compared to 1/100.000 cells in the bone marrow. Fat tissue is available in most patients and can be easily harvested with a minimally invasive surgical approach, offering a highly viable ASC popula-tion with optimal differentiation potential that is maintained with aging [3,9-12]. These cells can differen-tiate *in vitro* into several cell lineages, such as adipocytes, chondrocytes, osteoblasts, and myoblasts [2-5,13-19]. In addition, they secrete many bioactive molecules working as a sort of "mini-drugstore" that modulates the local immune response and creates an ideal regenerative environment [20-23].

The use of ASCs, either expanded or simply obtained by enzymatic treatment as SVF, created a huge interest and both *in vitro* and in vivo studies clearly demonstrated their anti-inflammatory and regenera-tive potentials [24]. Nevertheless, the prolonged ex vivo expansion may induce cell senescence and decline in multipotency, thus leading to clinical results below expectations. In addition, the majority of the pro-posed techniques have complex regulatory issues [25-27]. The increasingly urgent need to find new therapies for chronic, immunological and degenerative diseases prompted many investigators to search for tissue products containing progenitor cells, and, simultaneously, avoiding the several problems and restrictions related to the enzymatic manipulation and cell expansion [28,29]. In the last few years, we have been facing a significant number of studies aimed at the improvement of the therapeutic effects provided by the traditional fat transfer and structural fat grafting techniques [30-33]. In an effort to optimize this regenerative potential, MSC enrichment techniques, essentially based on enzymatic or mechanical devices, have been proposed [34,35]. In our experience, aminimally manipulated fat tissue is preferable, not only from a regulatory prospective [28,29], but mainly because of the biological rationale. Indeed, me-chanically derived MSC versus enzymatically isolated MSC have shown to have better differentiation potential [9,10], wider secretome36, and a large difference in exosomes contents [22,37,38]. The Lipogems® technology guarantees all of the requirements in an easy, quick, disposable device and represents a very promising "natural" approach in different fields [9,39-51].

Lipogems® Technology

The Lipogems®system incorporates a new technology to harvest, process and transfer adipose tissue. The technical part of the procedure is well described both in journal articles [9, 32,52] and in the web (https://www.youtube.com/results?-search_query=Lipogems+system).The resulting product is composed of small intact adipose tissue clusters (250-650 microns) and contains pericytes retained within an intact and biologically primed (by the mechanical trauma) stromal vascular niche. Based on the emerging clinical, scientific and regulatory requirements, the Lipogems® technology founds its effectiveness on some basic principles.

It is now well established that cells defined as MSCs exhibit substantial perivascular location and peri-cyte identity in vivo [53-55]. Pericytes are structural cells embracing the external wall of the microvessels and capillaries of the stromal vascular fraction of fat tissue and, after an injury such as inflammation or a damage of the vascular wall, they detach from the capillaries and gradually convert into activated re-generative MSCs [21,53,54]. Such pericyte-to-MSC activation entails the release (through exosomes) of re-generative factors and bioactive molecules which would make the transplanted Lipogems® product act-ing as a "personalized drugstore" [56]. The exquisite balance between an giogenetic, anti-inflammatory, immunomodulatory, anti-apoptotic, anti-microbial, mitotic, anti-scarring properties of MSCs allows a completely natural tissue repair and regeneration [36].

The second main characteristic of Lipogems® is related to the time-advantage. Indeed, the gentle me-chanical method allows obtaining a ready-to-use product in less than 20 minutes compared to the sev-eral hours, days or weeks required for the enzymatic digestion of the lipoaspirate and, possibly, *in vitro* cell expansion with substantial delay in the clinical application. In addition, Lipogems® is minimally manipulated according to the regulations set forth by the FDA. It received the FDA clearance as a class II medical device for processing autologous adipose tissue (5l0(k) first approval in US in December 2014 and new clearance in November 2016. Lipogems® qualifies as a 361 "HCT/P" (human cells, tis-sues, and cellular and tissue-based product) because it is autologous, minimally manipulated, intended for homologous use, enzyme free, not dependent on the metabolic activity of the cells for its primary function, used in the same surgical procedure, and not combined with anything other than saline.

The reduction of adipose cluster dimensions from 2-4,5 mm before processing to 0,3-0,7 mm of the fi-nal product, *maintaining a perfect structural integrity*, improves its ease of handling and post-transplant engraftment, due to the more effective and faster graft revascularization.

Several new promising fields of application are reported every month as this technique is spreading all over the world and have already received regulatory approval in 23 countries (http://www.lipogems.eu/index-eng.html).

Clinical Applications

Lipogemshas been shown to be absolutely safe and seems to work clinically much better than enzymat-ically isolated MSCs (both SVF or cultivated) as the preserved niche within a natural adipose scaffold works as the "perfect functional unit" [21,36].

In general surgery, Lipogems® has been used as a valid approach for the treatment of fecal incontinence and anal fistulas, showing impressive long term real morphological regeneration of muscle and neurological function [41,43,49,57].

In oncology, Lipogems®has been proved useful when injected in atrophied tissue after radiotherapy [58].

The regenerative potential in musculoskeletal diseases has been already analyzed, but more extended clinical trials are currently performed worldwide to confirm the first results [42, 46,48,50].

In orthopedic surgery, most patients with joint degenerative and inflammatory diseases may benefit of Lipogems® intra and peri-articular injection [59,60]. The intra-articular injection of Lipogems® for the treatment of osteoarthritis (accomplished with many European, Middle East and American colleagues), based on clinical results in thousands of patients worldwide, shows a surprising improvement of the symptoms. After injection of a variable quantity of Lipogems® (2-12 ml depending from the joint), pa-tients generally reported a brilliant immediate improvement of symptoms with long-term pain resolu-tion. In some cases, patients previously candidate for surgery, no longer needed it because of the com-plete or substantial resolution of their symptoms. Preoperative and post-operative X-ray and MRI com-parison showed a possible regeneration of the articular cartilage and a widening of the joint space 6 to 18 months after treatment. Moreover, the orthopedic use Lipogems® has also proved to be rewarding to foster repair in injured ligaments or tendons, in meniscal lesions, around surgical wounds, inside and around osteotomy gaps. These finding have been confirmed in Veterinary Medicine where Lipogems is becoming the leading regenerative therapy in polo horses and dog [61].

In plastic reconstructive surgery, Lipogems® helps the healing of chronic ulceration of the inferior legs and feet, above all in diabetic patients, with encouraging results. Only the vasculogenic properties of MSCs can explain these successes [62, 63].

The aesthetic surgery is a growing field of application. Lipogems® is used alone or in association with traditional surgical techniques such as facelift, blepharoplasty, breast augmentation and others. In the latter case, Lipogems® improves and accelerates wound healing and skin texture. Optimal results have been obtained in the periorbital area. After surgical intervention, the patients complain no pain, swelling or bruising, and are generally greatly satisfied. This treatment is often extended in a full-face bio-restoration aimed to define face contour, give it tone, new brightness and uniformity [64]. A recent publi-cation describes the use of Lipogems® during orthognathic surgery in 120 patients who underwent a double jaw intervention. Lipogems® was injected in multiple tissue planes and tunnels where the soft tissue lack had to be restored (mid face and mandible contours, neck, lips, chin profile). Results were compared to a series of patients treated with a traditional lipo filling technique. All the patients, except for 2, showed better enhancement of face morphology and skin texture, and much less post-operative swelling with consequently faster recovery [45].

Lipogems, MSCs and Future Horizons

Fat tissue transfer is a well established autologous method which has several clinical applications. The Lipogems® technology has been created to improve traditional grafting technique[9].

The most important and attractive feature of Lipogems® technology, and in general of MSCs, is the ability to naturally repair and regenerate certain types of tissue, such as joint cartilage, representing an ideal scaffold [40]. Recently, it has been demonstrated that exposure of Lipogems-derived MSCs to properly conveyed radio-electric fields was able to optimize stem cell expression of multipotency and lineage commitment at a remarkably higher degree than in enzymatically-dissociated MSCs obtained from the same donors65. This finding may significantly improve future cell therapy efforts [66].

Lipogems® technology fulfils the requirement to overcome the current limitations related to *in vitro* fat manipulation, making MSCs easily available within their natural 3D scaffold. It must be stressed that IFATS (International Federation for Adipose Therapeutics and Science) and ISCT (International Socie-ty for Cellular Therapy) recently established some clear definitions of Stromal Vascular Fraction and adipose-derived mesenchymal stem cells to better manage the future trials and to allows multicenter comparative studies [1,67,68]. We strongly believe that many of these trials should be compared to Li-po-gems® safety and effectiveness.

Conclusion

Adipose tissue is the ideal source for extracting but above all for using MSCs since (i) it can be easily accessed and harvested via a minimally invasive surgical procedure, (ii) it can be found in sufficient quantities in most people and (iii) it guarantees an adequate amount of progenitor cells with a good viability and minimally age-related differentiating potential.

The Lipogems® technology optimizes fat tissue natural properties. Without using enzymes, additives or centrifugations, but relying upon the use of mild mechanical forces, the Lipogems® system yields a mi-cro-fragmented product that behaves as a large-scale tool to supply damaged tissues with a regenerative environment. A number of randomized and controlled studies are now ongoing to strengthen its critical analysis and further develop and accelerate innovative therapeutic strategies and clinical protocols.

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