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Adipose Micrograft and Its Derived Mesenchymal Stem Cells with Their Exosomes in a Hyaluronic Acid Scaffold in Infiltrative Therapy in La Peyronie's Disease or Induratio Penis Plastica: A Pilot Study and Cases Report

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Abstract: The aim of this clinical study was to demonstrate that through a micrograft of viable adipose tissue of cells and its exosomes microfiltered at 35 microns to exclude fibrous shoots and cell debris in a suspension of hyaluronic acid were able to improve symptoms and clinical manifestations of Peyronye's curvature disease or IPP Induratio Penis Plastica with a beneficial effect also in plaques . Background and Objectives: Events leading to Induratio Penis Plastica (PPI) or Peyronie's disease may be discovered in an abnormal healing response within the tunica albuginea. From an anatomopathological point of view, Peyronie's disease derives from an excessive production of extracellular matrix deposited by fibroblasts with the formation of fibrotic tissue that leads to a retractile cicatricial outcome. The clinical course is characterized by an acute phase and a subsequent chronic phase with stabilization of symptoms. Events leading to Induratio Penis Plastica (PPI) or Peyronie's disease may be discovered in an abnormal healing response within the tunica albuginea. Materials and Methods: This study involved 12 patients with a history of symptoms characterized by curvature of the penis and painful erections were analyzed and subjected to this pilot study to verify the improvement of the anatomical area through a suspension containing 1.5 mL of viable micrografts from adipose tissue of cells and its exosomes in a 1.5 mL of hyaluronic acid evaluated by using a modified Vancouver scale. Results: The Modified Vancouver scales showed that with this technique it was possible to obtain excellent results both when the suspension was injected into plaques of Peyronie's disease when it was injected with the unique pomphs technique, with the intent to revitalize the tissue through progenitors with adult stemness markers. Conclusions: The combination of microfragmented and microfiltered adipose tissue of cells and its exosomes at 35 microns in a scaffold of hyaluronic acid is safe new method to treat Peyronye's disease or IPP Induratio Penis Plastica

Keywords: Peyronie's disease; IPP; adipose autologus micrograft; mesenchymal stem cells; exosomes; MicroSowing

1. Introduction

Peyronie's disease is a pathophysiological condition characterized by an abnormality in wound healing events. The events leading to the disease can be traced back to an abnormal healing response within the tunica albuginea [1,2] . The characteristic pathological aspect of Peyronie's disease

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derives from an excess production of extracellular matrix deposited by fibroblasts with the formation of fibrotic tissue which leads to a retracting scar outcome [3,4]. Clinically it is characterized by the presence of a pathological curvature on the shaft of the penis and consequent sexual dysfunction due to the sensation of pain. Among patients suffering from this condition, only a low percentage report having had a traumatic event during sexual intercourse [5,6]. The clinical course is characterized by an acute, very painful phase which induces a progressive curvature of the penis and a subsequent chronic phase with the stabilization of the symptoms. In this second phase, a slight improvement in symptoms may occur [7]. The signs, symptoms and therapy were described for the first time by Francois Gigot de la Peyronie in 1743 [8,9]. Although the disease can arise between the fifth and sixth decade of life, it can present itself at any age [10] with a notable impact on the couple's sexuality and the consequent quality of relationship life with the partner [11]. The treatment is different if the disease is in the acute or chronic phase or if deformation or "hinge" phenomena coexist, in which the penis bends on itself in the area of the deformity caused by axial pressure. The retracting plate must be identified by palpating the penis along its entire length, identifying the precise point or points of the positioning of the scarring (Photo 1) . A possible ultrasound study can complete the clinical evaluation by indicating the hemodynamics and dimensions of the plaque or plaques, allowing the appropriate therapeutic path to be activated [12,13].In patients with minimal complaints, a follow-up period and possible early pharmacological intervention are implemented which can also prevent the need for subsequent invasive treatment, such as surgical straightening of the penis. In this way, a less invasive approach is facilitated by the reduction of the plaque through an improvement in the quality of the fibroblasts implicated in the pathophysiological events with a consequent decrease in the deposition of fibrotic collagen [14,15].One of the usual least invasive treatments during both the acute and chronic phases is local infiltration therapy16 and refers to the process of injecting a drug directly into the plaque. This therapeutic approach represents a treatment modality with a very low invasiveness but with proven benefits [16] probably for the recovery of the circumference and length of the penile shaft [17,18]. A variety of agents have been studied in recent decades, including botulinum toxin, thiocolchicine, and hyaluronic acid. Hyaluronic acid has long been used to reduce symptoms and inflammation in PPI through intralesional injection and has been shown to reduce plaque volume and curvature due to its own intrinsic protective characteristics against reactive species of the oxygen and nitrogen generated during inflammation and limits their penetration especially to the cell membrane [19]. The aim of study is aimed at exploring a possible role also of adipose-derived Tissue Progenitors with the characteristics of adult mesenchymal stem cells as micrografts of vital tissue [20,21] using a hyaluronic acid as a scaffold20, 21 in the therapy of induratio penis plastica and to evaluate the efficacy and the safety of using this possible therapeutic approach also in the treatment of Peyronie's disease. Also , was to verify the possibility of using the possible therapeutic role of Tissue Progenitors with the characteristics of adult mesenchymal stem cells derived from viable micrografts from a sample of adipose tissue deprived of the inflammatory component through a simultaneous disaggregation and filtration [22] in the treatment of Peyronie's disease . Emerging therapies show that mesenchymal stem cells (MSCs) have immunomodulatory and antifibrotic effects by secreting regulatory miRNAs, proteins and exosomes with autocrine and paracrine activity with a consequent improvement in scarring due to the influence that some factors have in counteracting pro-fibrotic pathways [23] .

2. Materials and Methods

PATIENTS AND METHODS

The study was approved by the local Ethics Committee with authorization No.10143/2022 Uniroma . A total of 12 patients (aged between 21 and 78 years) were included in the study . The inclusion criteria were the following

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- history of symptoms characterized by curvature of the penis
- painful erections.

2.1. Exclusion Criteria

- History of mental disorders or emotional instability;
- History of allergic reaction to HA products;
- Current or previous (within 30 days of enrollment) treatment with an investigational drug and/or medical device or participation in another clinical study;
- History of mental disorders or emotional instability;

2.2. Procedure

The study was performed by following the standards of the local ethics committee, and in accordance with the Declaration of Helsinki (2000).

Patients were subjected to a injection of a suspension containing 1,5 mL of viable micrografts derived from adipose tissue [22] and emulsified in 1,5 mL of non cross-linked hyaluronic acid as a scaffold in the corpora cavernosa at the level of the plaque. The adipose tissue was extracted following a standardized protocol called MicroSowing . This standardized protocol guarantees the extraction of numerous Vital Tissue Progenitors of Side Population [22] . In fact, through some disposable devices it is possible to extract and process the optimal quantities of adipose tissue followed by the necessary microfiltration to the maximum size of the adipocyte tissue progenitors of 35 microns [24].

This microfiltration allows us to obtain a suspension containing only vital tissue progenitors, excluding all interfering material such as connective tissue and fragmented cell shells. The procedure for obtaining fat with the MicroSowing protocol involves four steps, as illustrated below; (1) :A regional site anesthesia is performed. (2) : The fat tissue is then removed. Both procedures are carried out through the use of a needle 18G or cannula multihole connected to a Luerlock® syringe of 10 ml to simplify the procedure (3) : The extracted tissue is immediately defragmented through a three-way valve to obtain a suspension containing the tissue progenitors. (4) The adipose tissue , during defragmentation , is microfiltered at a size of 35 microns to isolate the side population of tissue progenitors, excluding interfering material. The sterility of the entire procedure is guaranteed by the closed circuit in which the procedure takes place. The suspension thus obtained is mixed with 1.5 ml of non-cross-linked hyaluronic acid by connecting the two syringes. All of these procedures were carried out in a surgical theater

2.3. Detailed Procedure

After administering local anesthesia to the abdomen or supratrocanteric donor area With Klein's solution through a 10 mL syringe and a multi-hole cannula or a 18 G needle, the extraction of a total of 5 mL of lipoaspirate was undertaken (Photo 2) .

After adipose tissue extraction, 5 ml of saline was added to dilute the suspension and anesthesia fluids and the suspension was left to settle for 15 min, in order to eliminate all anesthesia fluids. Four ml of adipose tissue was processed as described by Tonnard 2013 [25] and filtered at 35 microns to preserve the Side population of tissue adipocyte progenitors22 (Photo 3) . The elimination of connective tissue and cell shells an debris by microfiltration allows to obtain a better therapeutic quality by excluding the interfering material with the ability to activate the toll-like system26 , obtaining a final suspension of 2.5 ml (Photo 4) . The microfiltrate is mixed with macromolecular hyaluronic acid through a three-way tap with a very gentle back and forth movement (made for 4-5 times) in order to emulsify the two parts and we identified the plaques (Photo 1) . The suspension

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thus obtained was injected directly into the plaques that are present along the corpora cavernosa with needle 30G (Photo 5). No patient complained of pain in the area of injection of the suspension. 30% reported mild to moderate pain for less than 10 days in the area of fat harvesting. Patients were discharged after 30 minutes of observation and evaluated one month, three months and 5 months after treatment.

3. Results

The patients underwent a baseline and dynamic penile ultrasound in the pre-treatment phase and at the 6-month follow-up. The study had as its primary outcome the degree of curvature measured with a goniometer during an erection pharmacologically induced with prostaglandins. As a secondary outcome, pain assessment was taken into consideration, using a VAS scale for the latter symptom (Table 1). Only 6 out of 12 patients reached 6 months of follow-up. In the 6 patients subjected to ultrasound control, an average reduction of 20% in the curvature angle was observed, while a clear improvement in painful symptoms was observed in all 12 patients already one month after treatment (Table 1)

Figures, Tables and Schemes

Figure 1. Physical examination to identify the plaque.

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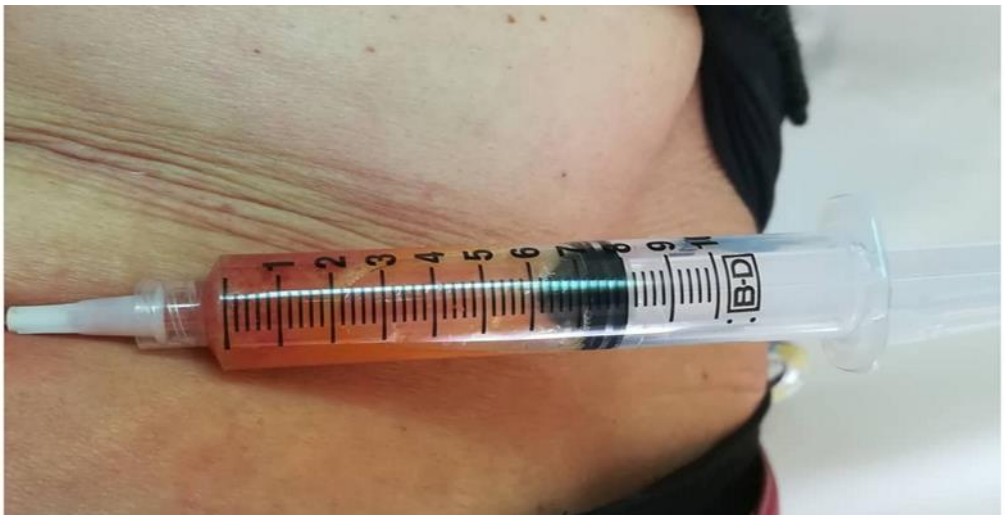

Figure 2. adipose tissue extraction with multi-hole cannula or 18 G needle after local anesthesia with Klein's solution . Note adrenaline-induced skin whitening.

Figure 3. Disaggregation of adipose tissue in the 10 ml syringe and simultaneous 35 micron filtration with harvesting in the 2.5 ml syringe.

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Figure 4. microfiltered adipose tissue.

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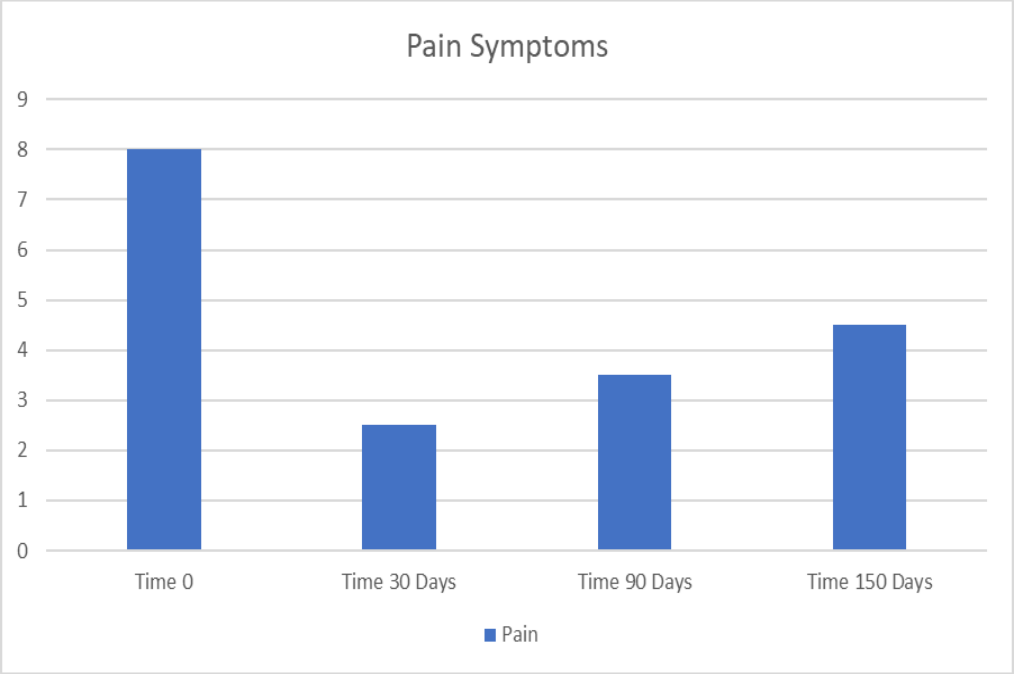
Figure 5. Injection of the microfiltrate in suspension with hyaluronic acid directly into the plaques of the penile shaft.

Table 1. Visual Analogue Scale of Intensity of pain during the follow up.



4. Discussion

Human mesenchymal stem cells (hMSCs) have been presented as a promising cell source for regenerative medicine in a variety of settings, including many adult tissues repair, and the use of Tissue Progenitors and its exosomes obtained from viable micrografts from adipose tissue with MicroSowing protocol conveyed by means of a non-cross-linked hyaluronic acid as scaffold supports the scientific hypothesis of a more complete and long-lasting suspension with the progenitors contained in it due to the ability of an activating action of CD 44 and protective action towards the other lineages of the mesenchymal/endothelial Clusters of Differentiation such as CD 73, 90 and 105 through the formation of protective niches [27] . The clinical hypothesis is that hyaluronic acid used as a scaffold in the treatment of PPI allows an improvement in physiological neo-collagenogenesis through the ability to react with the Clusters of Differentiation CD 44 present on the Progenitors and allows their survival in an environment hostile and inflammatory like that of plaques, as they are protected by an environment that allows the formation of niches by means of a viscoelastic scaffold. Additional markers present on the progenitors such as CD 73, 90 and 105 [22] would influence neo-vasculogenesis with consequent improvement in the intra- and perilesional vascularization of the plaque [28] . In order to improve a possible prevention strategy of an exclusively surgical chronic phase of this pathology, it has been postulated that this infiltrative method is mainly concentrated on the reduction of inflammation and hypoxia and both these mechanisms can be activated by the tissue Progenitors of adipose derivation and its exosomes [23] . In fact, although the etiology of Peyronie's disease is still uncertain today and consists of a chronic inflammation of the tunica albuginea due to the deficit in the physiological healing of wounds and deposition of fibrous components of the extracellular matrix in the soft tissue of the penis, in this context the capacity of the tissue Progenitors presents in the adipose microfiltrate thus obtained [22] which allows to favor the induction of regeneration factors through the up regulation of miR-144, miR-30, miR-150, miR-342, miR-29, miR223, miR-183 and miR-139 [23] in its exosomes [28] appears to be fundamental for controlling the progression of the disease. But the specific objectives include above all the analysis of the mechanisms of action of adipose-derived stem cells and its exosomes in the clinical context of induratio penis

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plastica and the identification of future prospects for the clinical application of this therapy. In fact, the positive effects of the use of MSCa in pathologies requiring tissue regeneration has already been demonstrated [22] . Adipose tissue contains numerous Tissue Progenitors with the typical markers of adult stem cells even when subjected to the disaggregation procedure according to Tonnard 2013 [25] and is an easily accessible source of sampling. The disaggregation of adipose tissue according to Tonnard 2013 allows you to have a tissue rich in progenitors but with the presence in suspension of fibrous shoots and potentially inflammatory cellular debris [22], for which a filtration of the disaggregated adipose at 35 microns [24] with the MicroSowing protocol , allows you to maintain a viable Side Population and numerically high [22] but almost totally free from the portion of tissue made up of deteriorated self [22] capable of activating the Toll-Like system 4 [26] and are able to secrete regenerative exosomes [28] . Adipose tissue, like other types of connective tissue, derives from mesenchyma, embryonic connective tissue and is rich in Tissue Progenitors with the typical markers of adult stem cells which can be extracted through the microfiltration procedure [25]. Tissue Progenitors or adult stem cells in adipose tissue are in fact very numerous, 1 in every 50 adipocytes, they are composed of small populations (average diameter = 17.9 μm) and large populations (average diameter 30.4 μm) and for this reason we have adopted limit of the size of the average diameters of large tissue progenitors [24]. No significant differences are evident regarding the morphology and immune phenotype of adult stem cells derived from bone marrow, umbilical cord and adipose tissue [25].

5. Conclusions

This retrospective clinical evaluation study for the treatment of PPI through a suspension of tissue progenitors from the side population with the characteristics of adult stem cells and the exosomes produced by them obtained with the MicroSowin technique in a scaffold of hyaluronic acid has provided excellent results through this method, with classic local injection therapy is a safe, effective and indicated procedure in patients suffering from Induratio Penis Plastica or Peyronie's disease. At the time of evaluation, 45% of patients reported improvement in curvature. The design of the definitive study, using a sample of larger patients and an adequate follow-up time, will provide further indications on the effectiveness of the procedure and on the possible need to repeat the treatment after some time.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Uniroma No. 10143/2022 on 24 June 2022.

Conflicts of Interest: The authors declare no conflict of interest.

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