

## Penile Enhancement Using Biodegradable Scaffolds Covered with Platelet-rich Plasma-Fibrin Glue, Mesenchymal Stem Cells for Micropenis

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**Purpose:** Evaluation of preliminary cosmetic and functional outcomes of biodegradable scaffolds covered with platelet-rich plasma in penile girth augmentation.

**Materials and methods:** Between June 2016 and June 2018, 36 males who had a mean age of 28.91 years (range 20 - 48 years) with micropenis underwent this procedure. A mixture of platelets-fibrin glue and mesenchymal cells obtained from dermal fat tissue were prepared. Then the mixture was seeded on the pretreated tube-shaped poly lactic-co-glycolic acid scaffold and underwent a whole day of incubation. Following penile degloving, scaffolds were surgically implanted within the interface region of dartos and Buck's fascia. The 5-point Likert scoring scale was used to evaluate the patients' satisfaction with surgery.

**Results:** Patients followed up for 6-12 ( $8 \pm 2.86$ ) months. The penile length in an erected state before surgery was 6.5 - 12.5 cm ( $9.08 \pm 1.6$ ) which enhanced to 7 - 14 cm ( $10.59 \pm 1.71$ ) after surgery ( $P < .0001$ ). The penile girth before and after surgery were  $8.49 \pm 1.53$  and  $10.91 \pm 1.96$  cm, respectively ( $P < .0001$ ). An augment in penile length and girth of 1.5 and 2.6 cm were achieved, respectively. Patients appraised surgical intervention on a rating of one to five. The highest possible score (5) was assigned by 27 %, 33 % expressed a very good mark (4), and 19 % gave a good mark (3).

**Conclusion:** Covering the scaffold with a mixture of Platelets-Fibrin glue and mesenchymal cells seems a safe and feasible method for penile reconstruction surgery. More studies should be done to determine the effect of platelets-fibrin glue and mesenchymal cells for treating micropenis.

**Keywords:** micropenis; girth enhancement; tissue engineering; platelet-rich plasma-fibrin glue; patients' satisfaction

### INTRODUCTION

Micropenis is defined as a penis that is abnormally small, typically less than 2.5 standard deviations (SDs) below the mean penile length for contemporary populations. Different etiologies can result in micropenis. The most common factors that cause this condition is the decrease in androgen production or decline in the androgenic effect before births.<sup>(1-3)</sup>

Psychological issues linked to a person's medical history are likely to harm their sexual quality of life if they have a micropenis. A number of issues that influence these patients include social and sexual worries, societal stigmatization, worry regarding infertility, painful therapeutic experiences, and low self-esteem.<sup>(4,5)</sup>

Autologous ex vivo tissue engineering process was first described in 2006 by Perovic et al.<sup>(6)</sup> The procedure included harvesting fibroblasts from the scrotal dermal tissue and seeding them into pretreated tube-shaped biodegradable scaffolds.

Cell-seeded scaffolds are commonly used in recon-

struction surgeries.<sup>(7)</sup> Covering the operative area with a broad coat of fibrin gel is the typical approach in soft tissue surgeries. The main benefit of platelet gel application is accelerating soft tissue healing. According to the literature review, platelets rich plasma (PRP) has been used successfully in urologic reconstruction surgeries.<sup>(8)</sup> PRP helps grafted fat survive and decreases fat absorption when used with autologous fat-free grafting for penile augmentation.<sup>(9)</sup>

In this study, we evaluated the effectiveness and safety of using a poly lactic-co-glycolic acid (PLGA) biodegradable scaffold covered with a mixture of platelets rich plasma-fibrin glue (PRP-FG) and mesenchymal cells for penile reconstruction and penile girth augmentation in males with micropenis. According to the well-known benefits of PRP in wound healing and its safety and effectiveness which are mentioned in the majority of previous studies, we hypothesized that a PLGA scaffold covered with PRP-FG and mesenchymal cells can be used for the treatment of patients with micropenis.

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**Table 1.** comparing the diameter and circumference of the penile shaft before and after surgery

Variable	Before surgery	After surgery	Size after – size before (cm)	P value <sup>1</sup>
Penile length (cm)	9.08 ± 1.6	10.59 ± 1.71	1.51 ± 11.17	< .0001
Penile girth (cm)	8.49 ± 1.53	10.91 ± 1.96	2.42 ± 0.84	< .0001

<sup>1</sup>Paired T-test

The following are the main goals of our research: to evaluate Complication rates, patient satisfaction levels, and changes in penis size, all following our surgical technique.

## MATERIALS AND METHODS

### Study Population

One hundred and eight men with micropenis (erected penile length < 2.5 SD from the mean penile length of contemporary) were initially referred to the urology clinic from June 2016 to 2018. The participants in the study expressed dissatisfaction with their penis size and received a clinical diagnosis of micropenis (**Figure 1**). They were referred for penile enhancement surgery.

### Inclusion and exclusion criteria

The following criteria were required for inclusion: 1) complaints of unsatisfactory penis size and a clinical diagnosis of micropenis; 2) age between 20 and 60; 3) understanding of the trial's protocols and written consent. Exclusion criteria included : 1) prior surgical penis extension procedures; 2) Cases with endocrine causes of micropenis including hypogonadotropic hypogonadism due to pituitary/ hypothalamic insufficiency and hypergonadotropic hypogonadism due to primary testicular insufficiency, and diabetic patients, history of psychiatric disorders, urethral abnormalities, high serum creatinine levels, erectile dysfunction, and cases with generalized atherosclerosis; 3) alcohol addiction. Finally, 36 men met all inclusion and exclusion criteria. They entered this prospective study.

### Ethical consideration

All patients provided written consent form prior to surgery. The study was approved by the ethics committee of Mashhad University of Medical Sciences (ethics code of IR. mums.FM.REC.1395.382).

### PRP-FG Preparation

After local anesthesia with plain 1% lidocaine, we made a thumbnail-sized oval-like cut to remove 0.5–1.0 cm<sup>3</sup> of cutaneous tissue. Biopsied tissue from the dermis was divided into pieces ≤ one mm, then dispensed over three 100 × 15mm Petri plates. The fibroblast cells were cultured in medium supplemented with platelet-rich plasma (PRP) until a total cell count of 2 × 10<sup>7</sup> was achieved. Fibroblast cells were cultured in Dulbecco's

Modified Eagle Medium, to which 8 percent platelet-rich plasma was added from the patient. The duration of the culture was 6 days, and three passaging were done.<sup>(10)</sup>

Platelets glue was prepared according to Shirvan et al.<sup>(11)</sup> methods. PRP gives the platelet concentration about 4-5 folds of the baseline in blood which is the optimum concentration for regeneration of tissue. Step 1) the blood (60 mL) was obtained from the peripheral venous sample incorporating 1.5 mL anticoagulant citrate dextrose solution. It was centrifuged at a 2000 rpm per minute (RPM) for 20 minutes. Supernatant plasma was separated and centrifuged at 3500 RPM for 8 minutes.

Twenty-five mL platelet-poor plasma was separated, and 5 mL concentrated PRP was left. The exact platelet concentration was between 1500-2250 × 10<sup>3</sup>/μL. Concentrated fibrinogen (5 mL) was prepared from 25 mL platelet-poor plasma by the biochemical method of cryoprecipitating.<sup>(12)</sup> The exact fibrinogen concentration was between 12-30 g/L. Step 2) Following a -70°C freeze and a 4°C thaw, plasma was centrifuged at 6500g for 5 Minutes. Concentrated PRP and concentrated fibrinogen were mixed.

### Liposuction method and Stromal Vascular Fraction

The liposuction materials were added to the 50-mL sterile tube and it was subjected to centrifugation at a speed of 3000 revolutions per minute for a duration of 10 minutes. The centrifuge process created 3 layers: 1. the upper layer (supernatant) contains adipose tissue. 2. Middle layer, which includes plasma. 3. The lower layer (pellet or precipitate) contains fat tissue-derived stromal vascular fraction (SVF), which includes mesenchymal fat tissue stem cells. SVF was mixed with PRP-FG. Adipose-derived stem cells (ADSCs) and PRP work together to promote revascularization (secrete more VEGF and raise the number of capillaries more effectively) and fat graft longevity.<sup>(13)</sup>

### Scaffold preparation and cell cultivation

Parched PLGA scaffold (Regen Biotech, chorea) length measures 50 mm, the internal diameter is 30 mm, and the thickness is 3 mm. The pore size ranges from 250 to 400 μm was immersed into a sterile 75% ethanol solution and maintained at a temperature of 4°C in a refrigerator throughout the night. SVF and PRP-FG

**Table 2.** impact of age, the diameters, and circumferences of penile shafts on complication

Variable	The group with complication (n=7)	The group without complication (n=29)	P value <sup>1</sup>
Penile length before surgery (cm)	9.07 ± 1.96	9.08 ± 1.54	.983
Penile length after surgery (cm)	9.5 ± 2.08	10.86 ± 1.54	.059
Penile length after-before surgery (cm)	0.42 ± 1.01	1.77 ± 1.06	.005
Penile girth before surgery (cm)	8.02 ± 1.38	8.6 ± 1.57	.379
Penile girth after surgery (cm)	10.22 ± 1.96	11.08 ± 1.96	.309
Penile girth after-before surgery (cm)	2.2 ± 1.24	2.47 ± 0.74	.449
Age (year)	30.28 ± 9.75	28.58 ± 7.17	.603

<sup>1</sup>independent T-test

**Table 3.** Scoring of the patients (n=36) to satisfaction from the surgery

Likert Scaling Scoring system	%
Score 1 (very bad)	2 (6)
Score 2 (bad)	3 (8)
Score 3 (good)	7 (19)
Score 4 (very good)	12 (33)
Score 5 (excellent)	10 (28)
Not participated in scaling scoring	2 (6)
Total patients	36 (100)

were added over the PLGA scaffolds (**Figure 2**) and they were maintained at 37 C with a 5% CO2 incubator over one day period.

For each person, two scaffolds of this size are used. Two passages are performed for fibroblast cells. The morphology of fibroblast cells is spindle-shaped, depending on the granule-free surface, and they are evenly distributed. Therefore, cell rounding, granulation, and separation from the bottom indicate unfavorable and unnatural growth conditions. Fibroblast cells are affixed to the scaffold by fibrin glue. Two PLGA scaffolds were inserted within the dartos muscle and Buck's fascia (**Figure 3**). Then the penis was dressed with an elastic bandage. The penile length and girth increased post-surgery (**Figure 4**). Following the injection, we anticipated angiogenesis in the lesion area, and a histopathological examination of the presence of inflammation or angiogenesis checked this.

#### Outcome assessment

The outcome, including changes in penile length and circumference after surgery, complications, and patients' satisfaction, were obtained and recorded in control visits three, six, nine, and 12 months after the surgical procedure. The length of the male penis was measured in a fully erect state before and after surgery. The penile vibratory stimulation method was used to fully erect the penis. In patients with a lack of response and satisfaction with penile vibratory stimulation, an intracavernosal injection of papaverine was used. The length and diameter of the penis were measured with a standard caliper before and after the intervention.

**Figure 1.** Patient with micropenis

Checklists and standard questionnaires were used to assess the level of patient satisfaction and complications following surgery. The questionnaire used a scoring system called the Likert scale with five points.<sup>(14)</sup>

#### Questionnaire of Patients with penile length and girth enlargement

Did you experience any issues getting an erection during your first sexual activity following the intervention? Have you ever experienced erection issues following treatment?

On a five point scale with 5 being the best estimate the results of surgical intervention (erect penile girth and length)/5-excellent, 4-very good, 3-good, 2-dissatisfactory 1-very dissatisfactory/?

#### Sample size

The sample size was calculated according to the Djordjevic study.<sup>(23)</sup> In this study, the mean scoring expressed by the patients according to the Likert Scaling Scoring system was  $4.3 \pm 0.8$ . Regarding the following formula and  $d = 0.3SD$ , the sample size was calculated as 42 patients.

#### Statistical analysis

The statistical software package SPSS version 25 (SPSS Institute, Inc., Chicago, IL, USA) was utilized to analyze the data. The experimental data are reported in the form of mean values with their corresponding standard deviations. One sample Kolmogorov-Smirnov test and Q-Q plot were used to define the distribution of variables. Paired t-tests, independent t-tests, and Fisher exact test were used for analysis. A statistical significance level was defined in the present study as a p-value below 0.05.

## RESULTS

After considering inclusion and exclusion criteria, of 108 patients with a diagnosis of micropenis, 42 patients entered the study. In the course of the study, six cases lost the follow-up. As a result, the final evaluation was performed in 36 cases. The mean patients age before surgery was 28.91 years (SD = 7.61, range = 20 - 48). The duration of follow-up was found to have a median of 6 (interquartile ranges of 6 -12) months. Complica-

**Figure 2.** Scaffolds made of PLGA were covered with SVF and PRP-FG.

**Table 4.** Patient satisfaction scores from the surgery in complicated vs. non-complicated cases

Scoring	Patients with complication N (%)	Patients without complication N (%)	P value <sup>1</sup>
Score bad (scores 1 & 2)	5 (71)	0 (0)	<.0001
Score good (scores 3-5)	2(29)	27 (100)	
Total cases	7(100)	27 2 (100)	

<sup>1</sup> Fisher exact test. <sup>2</sup> Two patients did not participate in scale scoring

tions were reported in 7 cases (19 %), including infections (3 cases; 8 %), severe penile edema (2 cases; 5 %), painful erection (one patient; 2 %), the suture opening (one patient; 2 %).

Two patients with infection were effectively cured with oral antibiotics. These two patients were given metronidazole (500mg, three times a day, orally, ten days) and cephalexin (500mg, every six hours, orally, ten days). Systemic antibiotics did not control local infection in one patient (2 %), and removal of the scaffold was needed. Two cases with penile edema were managed conservatively; they did not experience any long-term effects from penile edema.

The penile length and girth before and after surgery were compared (Table 1). The differences in penile length and girth after and before surgery (cm) were measured. Despite the homogeneity of variance, all quantitative variables had a normal distribution. The duration of follow-ups was 6 and 12 months in 24 (2/3) and 12 (1/3) cases, respectively.

The average length of the male penis in a fully erect state before surgery was 9.08cm (SD = 1.6, range = 6.5 - 12.5) which reached the mean of 10.59 cm (SD = 1.71, range = 7-14) after the surgery ( $P < .0001$ ). The mean penile girth before and after surgery were  $8.49 \pm 1.53$  and  $10.91 \pm 1.96$  cm, respectively ( $P < .0001$ ) (Table 1). An augmentation in penile length and girth of 1.5 and 2.6 cm were achieved by surgery.



**Figure 3.** Two PLGA scaffolds were placed within the Buck's fascia and dartos muscle.

The impacts of age, penile diameter, and circumference on inducing complications were evaluated by paired T-test. The age of the patients, diameters, and circumferences of penile shafts before and after surgery had no significant impact on complications ( $P > .05$  for all) (Table 2). Sixty one and three tenths percentage and 19 % of patients expressed very good, excellent (scoring of 4 & 4) and good (scoring 3) scoring with erect penile girth, respectively (Table 3).

A good score (score 3-5) on the results of the surgery was given in a significantly higher number of patients without complications versus those with complications ( $P < .0001$ ) (Table 4). The severity of the patients' initial condition and the length of time since surgery influenced patient satisfaction. The milder the severity of the initial condition and the shorter the time since the surgery, the higher the level of patient satisfaction.

**DISCUSSION**

In this study, we applied the principle of adding SVF and PRP-FG on the biodegradable scaffold that provides appropriate mechanical strength to induce the three-dimensional growth of new functional vascularized loose connective tissue. This tissue consists of a few widely dispersed fibroblasts, a small amount of fibrillar collagen, and a few collagen fibers interspersed with the muscle fibers.<sup>(15,16)</sup> The operation was proven effective at boosting penile size and length.



**Figure 4.** Penis Post- surgery

The well-known benefits of PRP for wound healing serve as justification for its use. The bioactive components of platelets are found in dense granules and  $\alpha$ -granules. Growth factors and cytokines such as insulin-like growth factor, transforming growth factor- $\beta$ , and platelet-derived growth factor are found in the  $\alpha$ -granules. These cytokines and growth factors have essential functions in angiogenesis, chemotaxis, and the differentiation of cells.<sup>(17)</sup>

A fibrin clot created by FG is around ten times more potent than a physiological clot. This clot act as a robust provisional matrix, enabling local fibroblast proliferation, the production of collagen, and following substitution by connective tissue, the paracrine inflow of immune cells, and avoiding the development of fibrosis.<sup>(18,19)</sup>

A scaffold is needed to transfer the cells to the lesion site. The optimal tissue engineering scaffold should be biocompatible, simple to utilize, and able to be fixed in the lesion. In addition, have a high porosity and linked pores that permit the growth and differentiation of stem cells, the entry and exit of substances, a high degradability rate in the body, and the capacity for rapid angiogenesis.<sup>(20,21)</sup>

The biodegradable scaffolds' propensity to absorb virtually entirely after implantation is one of its key features. Local tissue ingrowth gradually replaces the scaffold until it finally becomes unnecessary. An additional advantage is the scaffolds' inclination to facilitate cell proliferation. The fact that scaffolds are mostly made of matrix proteins, which have the potent ability to direct and encourage the ingrowth of many cell types, is one of the causes of the potential for cell proliferation.<sup>(22-24)</sup>

In penile girth enlargement surgery for persons experiencing micropenis, the use of a biodegradable scaffold comprising of polyacid-co-glycolide material (Maxpol-T) coated with autologous fibroblasts was reported by Jin and coworkers.<sup>(22)</sup> The participant's ages ranged from 19–52 ( $33 \pm 9.14$ ) years old, including 8 out of 69 cases (11 %) with hypogonadism. The mean pre-surgical penile girth was  $8.18 \pm 0.83$  cm in the flaccid condition and  $10.26 \pm 1.22$  cm in the erect condition, respectively.<sup>(22)</sup>

At the 6-month assessment, the average circumference of the penis in its flaccid and erect forms demonstrated a notable increase to  $12.19 \pm 1.27$  cm and  $13.18 \pm 1.31$  cm, correspondingly. Following surgery, there was a profound rise in circumference of penis in both flaccid and erect condition ( $P < .001$  for both). Overall penile girth increased at least 2 cm after surgery in 95% of patients. Moreover, they reported a low postsurgical complication (8 %) and very good and good patient satisfaction scores in 84 % and 10 % of cases, respectively.<sup>(22)</sup>

Like the study by Jin et al.<sup>(22)</sup>, we found a substantial change in penile girth following surgery. In Jin et al.'s (19) study 95% of individuals showed an increased penile girth of at least 2 cm. Complications were noted in 6 (8 %) of patients, including prolonged subcutaneous edema lasting about 12 weeks ( $n = 3$ ; 4 %) and tiny abrasion near the suture ( $n = 3$ ; 4 %). Like Jin et al.<sup>(22)</sup>, we found a considerable rise in penile girth after intervention. In contrast to our results which indicate a remarkable increase in the penile length, they did not observe any appreciable change in penile length after procedure ( $P > .05$ ).

Casavantes et al. (25) reported 729 men with 2–3 ses-

sions of polymethylmethacrylate (PMMA) injection, who reached an average gain in flaccid penile length and girth were 2.21 (SD = 1.16) and 0.7 cm, respectively. Patients' satisfaction with the post-surgery outcomes was 83%. Sadly, 52 % of patients reported irregularities such as any number of nodules, including tiny ones at the entrance points and indentations.

Casavantes et al.'s study<sup>(25)</sup> had a higher rate of complications in comparison to our study (52% versus 19 %, respectively). There was more increase in average penile length in our study compared to Casavantes et al. (1.5cm versus 0.7cm, respectively). Also, an increase in average girth was more in our study compared to Casavantes et al. (2.6 cm, 2.21, respectively). One of the limitations of Casavantes et al.'s study is that many of the PMMA products are very expensive.

Elist et al.<sup>(26)</sup> used a silicone subcutaneous penile implant (Penuma®). Outcomes of 400 patients enhancement in the mid shaft width of 56 %, from an average pre-surgical girth of  $8.5 \pm 1.2$ cm to an average pre-surgical of  $13.4 \pm 1.9$ cm ( $P < .001$ ), after an average of 4 years. Compared to our study, in which the mean penile girth before and after surgery were  $8.49 \pm 1.53$  and  $10.91 \pm 1.96$  cm, respectively ( $P < .01$ ). They also informed an increase in penile length from the preoperative  $9.1 \pm 0.7$ cm to the postoperative  $11.3 \pm 0.4$ cm ( $P < .01$ ). Elist et al.<sup>(26)</sup> evaluated only flaccid penile length. Compared to our study, in which the average penile length when erect before surgery was  $9.08 \pm 1.6$  which reached the mean of  $10.59 \pm 1.71$  cm after the surgery ( $P < .001$ ). Elist et al. (26) mentioned a low incidence of complications: Seroma (4 %), wound development (4 %), and infection (3 %) were the most commonly cited postsurgical complications. Three percent of patients developed adverse events that required device removal. Overall, Penuma® received excellent patient feedback.

The authors used Augmentation Phalloplasty Patient Selection and Satisfaction Inventory (APPSSI) questionnaire to appraise patients' satisfaction with the device.<sup>(26)</sup> Great or extremely great levels of satisfaction were revealed by 81% of patients. Elist et al.<sup>(26)</sup> had a larger sample size (400 patients) and longer follow-up duration (4 years) compared to our study, which included 36 patients and averaged an 8-month follow-up time. Penile seroma occurred in 19 (4 %) patients in their study, but none in ours. Complications requiring device removal were reported in 12 (3%) of their patients and in one (2 %) of ours, due to infection. Elist et al.<sup>(26)</sup>'s study has a number of drawbacks. It is Retrospective and The APPSSI questionnaire is not a verified investigation.

Twenty-one patients, aged 22–37 (mean 28), received a repeated penile girth enlargement surgery using biodegradable scaffolds in the study by Djordjevic et al.<sup>(27)</sup> Two PLGA scaffolds seeded with fibroblasts from specimens of scrotal tissue were inserted as part of the procedure. Men who underwent repeated surgery showed a statistically significant improvement in girth increase compared to those who had only one surgery ( $P < .001$ ). There are concerns for repeated penile girth enhancement procedures with biodegradable scaffolds in long term follow up.

***We are conscious of some restrictions in this research that need to be taken into account***

1. This study has a small sample size, and placebo or control groups do not exist.

2. The effects of this kind of treatment appear in the long term. Due to the cumulative effects of paracrine and autocrine mechanisms.

3. Due to the short follow-up, no firm conclusion can be drawn.

4. The concentration of the cocktail of growth factors in PRP varies in men, and this may affect the quality of cell proliferation and their potency for tissue regeneration.<sup>(28)</sup>

More studies with a control group are required to support the use of PRP as a treatment for micropenis. Also, we recommend measuring the concentration of growth factors and cytokines in future PRP studies.

## CONCLUSIONS

Using a scaffold covered with a combination of PRP-FG and mesenchymal cells is a feasible method for penile reconstruction surgery. Complications needing scaffold removal were uncommon in our participants. This significantly less invasive approach with a high success rate and easy technique offers patients and surgeons the potential for positive outcomes.

## SUMMARY

This study showed that using a scaffold covered with a combination of PRP-FG and mesenchymal cells is a feasible method for penile reconstruction surgery. The penile length and girth increased significantly after surgery ( $P < .05$ ).

## FUNDING

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## CONFLICT OF INTEREST

The authors assert that they do not have any competing interests to declare pertaining to this study.

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