



## Adjuvant measures and genetic evaluations to improve results of hair transplantation

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### ABSTRACT

Follicular unit extraction (FUE) has evolved dramatically as the most recent advancement in surgical hair restoration as it leaves a tiny scar and creates natural and pleasing results. This study aims to show the effectiveness of adjuvant measures and genetic evaluations in improving outcomes. Prospective analysis of 271 male patients with androgenic alopecia who underwent hair transplantation with FUE technique between August 2015 and February 2020 at our center was conducted. The mean age was  $35.93 \pm 4.40$  years. At one year postoperatively, patients were asked to fill up a questionnaire which included their satisfaction level, need for 2nd session, and complications. Informed written consent was obtained from all patients. Also, blood samples were provided from patients before the operation. RNA extraction and cDNA synthesis were performed using the RNX-Plus kit (Cinnagen, Iran) and Vivantis kit (Malaysia). Amplification of SRD5A2 and GAPDH genes (as internal standard) for measuring gene expression was performed by real-time PCR. Data were analyzed using the statistical package for social science SPSS V. 23. In the last 156 cases, the addition of 40 mg of Triamcinolone to the LA solution led to a dramatic reduction of the incidence of postoperative oedema, from 40% to 9%. Adding three sessions of PRP at 2nd, 4th and 6th months postoperatively resulted in an increased patient satisfaction rate with better hair density and thickness where the rate of highly satisfied patients increased from 64.5% to 83.7%. The addition of 40 mg Triamcinolone to the LA solution was highly effective in reducing postoperative oedema. Three sessions of PRP at 2<sup>nd</sup>, 4<sup>th</sup> and 6<sup>th</sup> months postoperatively were recommended. The results of SRD5A2 gene expression showed that the expression of this gene in satisfied ( $P = 0.049$ ) and dissatisfied ( $P = 0.028$ ) patients were significantly higher than highly satisfied patients, which means that the SRD5A2 gene expression had an essential role in the successfulness of hair transplantation. The increased expression of this gene could reduce the response to hair transplantation.

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### Introduction

Alopecia may result in considerable psychological disturbances and low self-esteem (1). Androgenic alopecia (AGA) is characterized by progressive visible thinning of scalp hair in genetically susceptible men and some women (2). Hair replacement surgery appears to date back to Japan. An article by Okuda in 1939 (3) was the first that used self-made sharp circular punches in various diameters (1-4 mm), but Orentreich (4) in 1959 popularized the concept of hair transplantation for treating baldness, however; the grafted hair, done with large punch gave a plug-like unnatural appearance. Hair transplantation has gone through a big revolution with the pioneers in this field (5-7). Follicular unit extraction (FUE), first described in 2002 by Inabas (8), has evolved dramatically as the most recent advancement in surgical hair restoration

as it leaves a little scar and creates natural, and pleasing results. (9, 10) Success with FUE depends on being able to predictably dissect excellent-quality grafts with minimum transaction rates from the donor site. (11, 12) In the last three years we added some adjuvant measures in the FUE method that improved our results in hair transplantation.

For many years, scientists have believed that the dominant male sex hormone testosterone causes androgenetic alopecia, in which women usually have low levels of this hormone (13). But, nowadays, they have conducted that dihydrotestosterone (DHT) is the leading cause of androgenetic alopecia (14). DHT is derived from the male hormone testosterone and is the enemy of hair follicles (15). Under certain conditions, DHT can inhibit hair follicles from producing hair. This simple process is the cause of many hair loss

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types (16). Testosterone is converted to DHT by the enzyme 5-alpha reductase (17). The SRD5A2 gene provides instructions for making steroid 5-alpha reductase 2, and mutations in this gene prevent steroid 5-alpha reductase-2 from converting testosterone to DHT in the developing reproductive tissues (18). Therefore, changes in structure and amount of this gene expression could cause baldness (17). Although many studies have been conducted on the expression of the SRD5A2 gene and its role in hair loss (19), the effect of this gene on the performance of hair transplantation has not yet been determined.

This study aims to show the effectiveness of the adjuvant measures in improving our results for increasing patient satisfaction and considering the effect of SRD5A2 gene expression on hair transplantation.

## Materials and Methods

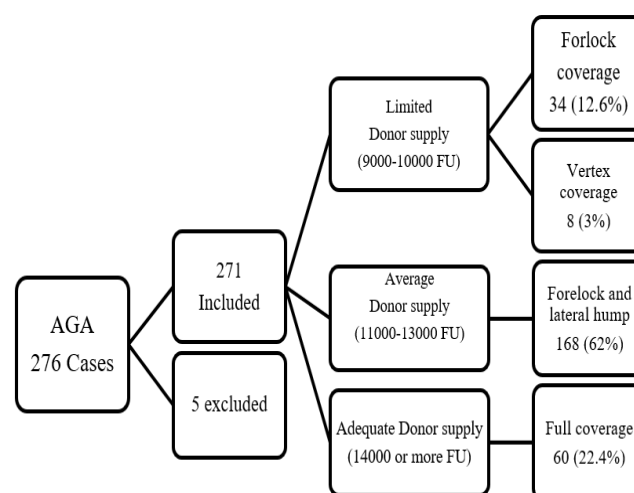
### Patients

Prospective analysis was conducted on 276 patients with AGA who underwent hair transplantation with FUE technique between August 2015 and February 2020 at CMC private hospital, Erbil-KRG, Iraq. The mean age was  $35.93 \pm 4.40$  years, ranging from 29-43 years. Inclusion criteria were male patients with AGA, good donor site, realistic expectations, and good body health, and exclusion criteria was female patients, unrealistic expectations, patients with AGA and inadequate donor hair density, other causes of alopecia, patients with associated medical diseases, and 5 cases excluded because of lack of follow up (the remaining 271 cases enrolled in the study).

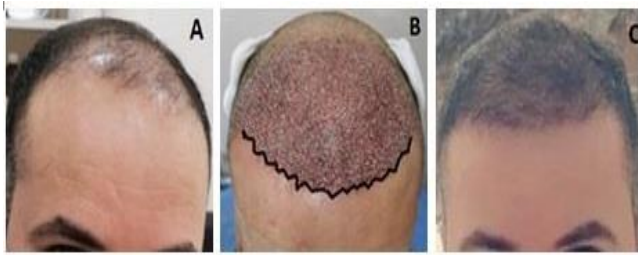
### Procedure

After the counseling session with the patients, the process of AGA pattern hair loss, different management options, explanation about the FUE procedure, possible postoperative complications were explained. Also, it was explained that the final result will not be seen before 9 months, and postoperatively should continue on minoxidil shampoo indefinitely to preserve existing hair. Then, the donor site was assessed for density and hair quality. Any patient with donor site density less than  $80 \text{ FU/cm}^2$  was considered unsuitable for hair transplantation. The donor site was selected between the occipital protuberance and 1 cm above the top of the ear. Extraction was limited to

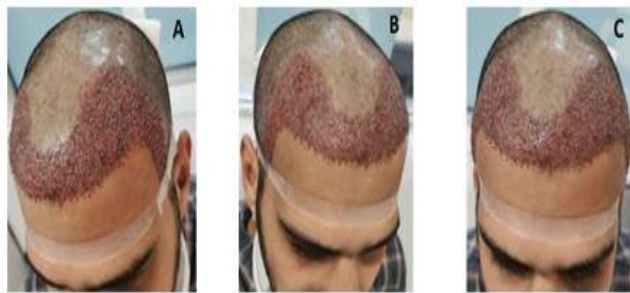
25% of the donor hair available. A plan formulated was based on the amount of donor's hair available and the desired coverage area expressed by the patients (Figure 1). Therefore, patients with limited donor area offered frontal forelock (Figure 2) or vertex was accepted only while patients had average donor area offered forelock and lateral hump coverage (Figure 3) and patients with adequate donor hair offered full coverage (Figure 4). The patients underwent routine laboratory blood investigations like CBC, coagulation profile, and viral screen tests. All patients were advised to have a preoperative shampooing of the scalp with chlorhexidine gluconate the night before and the morning of surgery. The patient's hair was trimmed short before the surgery. Analgesics and antibiotics were administered at the start of surgery. Strict surgical asepsis was followed. Marking was done to determine the height of the anterior hairline (AHL) (Figure 5). The location of the most anterior, midfrontal portion of the hairline was marked 8.5-10 cm above the glabella. A gently curving hairline was created with care taken to maintain a significant frontal-temporal recession. Then, marking was done for the lateral hump (Figure 6). This landmark is important because it represents the lateral extent of the AHL. For donor area marking, the region between the occipital protuberance and 1 cm above the top of the ears was considered the safe donor site.



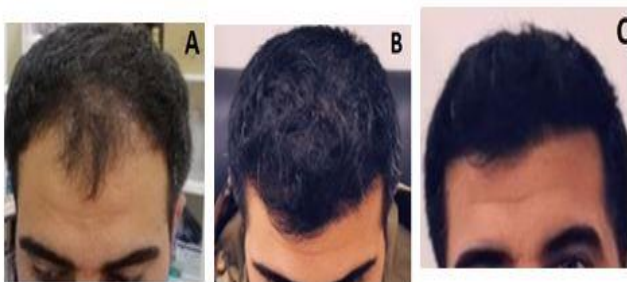
**Figure 1.** The flow diagram that shows the plan for the recipient coverage based on the amount of donor supply (AGA: androgenic alopecia, FU: Follicular unit)



**Figure 2.** 42-year-old patient with Norwood grade 5 baldness, planned for Frontal forelock coverage because of limited donor supply. A: Preoperative, B: Intraoperative with frontal forelock coverage with 2150 FU grafts in one session using FUE method note zigzag frontal hair line, C: One year post-operatively note the irregularity of the frontal hairline and the distribution of grafts containing 1-2 hair per FU at the leading edge with larger grafts posteriorly contribute to the natural appearance of the hair transplantation.



**Figure 3.** 38-year-old patient with Norwood grade 4 baldness, planned for Frontal forelock and lateral hump coverage because of average donor supply, with 2660 FU grafts in one session using FUE method. A,B,C: Intraoperative left oblique, right oblique, and frontal views respectively.



**Figure 4.** 33-year-old patient with Norwood grade 4 baldness, planned for full coverage because of adequate donor supply, with 3050 FU grafts in one session using FUE method. A: Preoperative, B and C: One year postoperatively. Note: this patient received three sessions of PRP at 2<sup>nd</sup>, 4<sup>th</sup>, and 6<sup>th</sup>-month post operatively, leading to excellent natural results with full coverage with denser, thicker and shiny hair and improvement of the preexisting hairs.



**Figure 5.** The most important landmark that needs to be determined is the height of the anterior hairline (AHL), the location of the most anterior, midfrontal portion of the hairline was marked 8.5- 10 cm above the glabella (A,B,C preoperative). The shape of the frontal hairline broken up with triangles and gaps to give zigzag appearance to get natural result (D, E and F One week postoperative).



**Figure 6.** (A and B): The lateral hump. This landmark is important because it represents the lateral extent of the AHL

### Anesthesia

FUE was performed under local anesthesia. The local anesthesia solution was a 40 ml mixture of 0.25% bupivacaine with 1:200,000 epinephrine + 20 ml 1.0% lidocaine with 1:200,000 epinephrine and in the last 147 cases, 40 mg of Triamcinolone was added to the solution. supraorbital and supratrochlear nerve blocks were given to anesthetize the recipient area. Ring block anesthesia was administered to the recipient and donor area. This was followed by the tumescent injection to the whole donor area and recipient site.

### Donor site harvest

Follicles were extracted using micro motor punches with sharp small punches (0.8-1.1 mm in diameter), from the safe donor area; the net result was the isolation and removal of a single FU. Once the FU

was harvested, the tissue was immediately immersed in chilled isotonic saline and the donor site punctures were left to heal by secondary intention.

### Recipient site creation

We used a 19-gauge needle that produce a 1.1 mm slit and accommodate the size of the majority of FU. Sometimes we used customized recipient blades cut to a specific size from surgical prep blades. The angle of the recipient slit was parallel to the angle of the existed hair.

### Graft planting

Two assistants worked simultaneously and planted FU grafts using forceps of microsurgery, did gentle grasping of the FU grafts, placed the grafts in the identical angle of slit creation. Each time put a small amount of FU grafts was put on their gloved hand so that they can be planted within 4-5 minutes to decrease the warm ischemia time of the FU grafts. The shape of the frontal hairline was broken up with triangles and gaps (Figure 2 and 5) consisting of random placement of single hair grafts from the softest hair available in donor supply. Posterior to the single hair grafts putting FU containing 2 and 3 stronger hairs.

### Post-operative

All patients were received postoperative oral antibiotics and analgesics and instructed about head elevation and applying a cold gel pad to the forehead and donor area. Gentle shampooing commenced on the 2<sup>nd</sup> postoperative day. Patients were followed up on the 3<sup>rd</sup>, 7<sup>th</sup> and 14<sup>th</sup> day, and then monthly for up to six months then after 1 year postoperatively. In each visit, the patients were checked for any possible complications and managed accordingly. In the last 152 cases, three sessions of PRP were done at the 2<sup>nd</sup>, 4<sup>th</sup> and 6<sup>th</sup> months, postoperatively using (YCELLBIO PRP Kit) and the single spin method at 1500 rpm for 5 minutes. Following the centrifugation (Figure 7), the sample was separated into three layers including the yellow top layer (plasma), a thin middle layer, the buffy coat (PRP), and a red bottom layer (RBC). Then, the buffy coat was transferred to an empty syringe and from each Kit, we received 1.5 ml of PRP, so by using two Kits we received about 3 ml of PRP. After that, the PRP was mixed with an

activator (calcium chloride) and mixing was done by 20-time quick transferring between two 10 ml syringes. Then, the activated PRP was injected to the recipient site intradermally at 0.1 ml/cm<sup>2</sup> in a linear pattern one cm apart from a depth of 2-3 mm.

At one year, patients were asked to fill up a questionnaire that included their satisfaction level on a three-point scale (dissatisfied, satisfied, highly satisfied), need for the 2<sup>nd</sup> session, and complications.

### Genetic evaluations

From 271 participants in this study, 3ml of blood samples were taken to extract RNA. RNA extraction and cDNA synthesis were performed using the RNX-Plus kit (Cinnagen, Iran) and Vivantis kit (Malaysia). Amplification of SRD5A2 and GAPDH genes (as internal standard) for measuring gene expression was performed by real-time PCR. Primer design for these two genes was done using Primer Express and Gene runner software. The primers were made by Remington and Winchester Company, USA. The sequences of primers are shown in Table 1.



**Figure 7.** PRP: Following the centrifugation, the sample is separated into three layers, the yellow top layer (Platelet poor plasma PPP), a thin middle layer, the buffy coat (PRP), and a red bottom layer (Red blood corpuscles RBC).

**Table 1.** Sequences of primers for SRD5A2 gene and GAPDH gene in Real-time PCR

Genes	Primer Sequence	Accession No. (Ref. Seq)
SRD5A2 Forward	5'-AACACGGCGCGATGCAGGTT-3'	NM_000348.3
Reverse	5'-CCGTGTGCTTCCCGTAGCCG-3'	
GAPDH Forward	5'-CAAGGTCATCCATGACAACCTTTG-3'	NM_002046.3
Reverse	5'-GTCCACCACCCTGTTGCTGTAG-3'	

The final volume for each reaction was 20 µl, which included 100 ng of Power SYBR® Green PCR Master, 1 µl of cDNA, 10 µl of Mastermix (Applied Biosystems, USA), 1 µl of forward primer, 1 µl of reverse primer, and 7 µl of free nuclease water. Temperature protocol was as primary denaturation at 95°C for 3 minutes, followed by 45 cycles as denaturation at 95°C for 5 seconds and annealing at 60°C for 30 seconds. Formula  $2^{-\Delta\Delta CT}$  was used to measure gene expression.

### Ethical considerations

The study protocol was approved by the Medical Ethics Committee of the College of Medicine of Hawler Medical University. Informed written consent was obtained from all patients.

### Statistical analysis

Data were analyzed using the statistical package for social science SPSS V. 23. The Chi-square test of associates was used to compare between proportions. Fisher exact test was used when the expected count of more than 20% of the cells of the table was less than 5. A P-value of less or equal to 0.05 was considered statistically significant.

### Results and discussion

The severity of androgenic alopecia was Norwood III, IV, V, and VI in 30(11.1%), 71 (26.2%), 156(57.6%), and 14(5.2%) patients, respectively. A total of 728,800 FU grafts were transplanted in 271 cases with the FUE method. The minimum amount was 2000 FU grafts, and the maximum was 3400 FU grafts, with a mean of  $2930 \pm 412.91$  SD FU grafts. The incidence of postoperative edema in relation to adding Triamcinolone to the LA solution is shown in Table 2. Table 2 shows a significant decrease in postoperative edema after adding Triamcinolone to the LA solution with a highly significant P-value. Table 3 shows that the proportion of highly satisfied patients was significantly increased after adding PRP sessions with a P-value of 0.026, where the rate of the highly satisfied patients was increased from 64.5% to 83.7% with a P-value of 0.026 which was statistically significant. PRP is rich in many growth factors and proteins.

Table 4 shows the frequency of donor site complications, and Table 5 shows the frequency of recipient site complications.

**Table 2.** The incidence of postoperative edema in relation to adding Triamcinolone to LA solution

Triamcinolone in LA solution	Post-operative oedema				Total	P-Value
	NO Oedema	Upper forehead oedema	Upper and lower forehead oedema	Periorbital oedema		
NO	69 60%	23 20%	17 14.8%	6 5.2%	115 100%	0.000
YES	142 91%	9 5.8%	5 3.2%	0 0%	156 100%	
Total	211 77.9%	32 11.8%	22 8.1%	6 2.2%	271 100%	

**Table 3.** Patient satisfaction at one year postoperatively in relation to the addition of three PRP sessions at 2<sup>nd</sup>, 4<sup>th</sup> and 6<sup>th</sup> months post-operatively

PRP Postoperatively	Patient satisfaction			Total	P-Value
	dissatisfied	Satisfied	Highly Satisfied		
NO	7 5.6%	37 29.8%	80 64.5%	124 100%	0.026
YES	2 1.4%	22 15%	123 83.7%	147 100%	
Total	9 3.3%	59 21.8%	203 74.9%	271 100%	

**Table 4.** Frequency of donor site complications

Donor complications in FUE Method	No complications	Donor hair effluvium	Cyst	Total
Frequency	258	11	2	271
Percent	95.2%	4.1%	0.7%	100%

**Table 5.** Frequency of recipient site complications

Recipient complications	No complications	Recipient effluvium	Folliculitis	Cyst	Crusting	Total
Frequency	221	9	20	8	13	271
Percent	81.5%	3.3%	7.4%	3%	4.8%	100%

In an attempt to improve our result of hair transplantation, we added three sessions of PRP at 2nd, 4th and 6th months postoperatively using (YCELLBIO PRP Kit.), which resulted in an increased patient satisfaction rate with better hair density and thickness. The low incidence of donor effluvium in our study could be due to the limiting extraction rate to 25% of FU (Figure 8).

### Genetic evaluation results

One year after hair transplantation, out of 271 participants in this experiment, 203 (74.9%) had high satisfaction with the operation, 59 people (21.8%)

were satisfied, and 9 people were dissatisfied with the operation. The results of SRD5A2 gene expression showed that the expression of this gene in satisfied ( $P = 0.049$ ) and dissatisfied ( $P = 0.028$ ) patients is significantly higher than highly satisfied patients (Figure 9).

Male type baldness harms an individual's self-esteem and emotional well-being. Hair transplantation gives a permanent solution for those patients (20, 21). Hair transplantation is a relatively new and continuously evolving art, with several new advances, leading to more natural results for patients (22-24). Successful hair transplantation needs the adequate experience of the surgeon and staff, excellent lighting, using loupe magnification, adhering to sterile precautions, using proper instruments, and proper patient selection. We selected male patients with AGA and acceptable donor hair density and quality. We avoided patients with AGA and inadequate donor hair density, patients with other causes of alopecia, patients with unrealistic expectations, and patients with associated medical diseases. Because of the progressive nature of male-pattern baldness, patients who request inappropriate low hairline should be rejected for hair transplantation because they are unrealistic and would be dissatisfied later when the progressive hair loss during the next decade leads to the bizarre appearance of the low hairline (25-27).

We planned to determine the amount of recipient coverage according to the amount of donor supply and the patient's desire (Figure 1). Any patient with a donor supply of less than 8,000 FU was rejected for hair transplantation. Patients with limited donor supply offered frontal forelock or Vertex only while patients with average donor supply were offered forelock and lateral hump coverage and patients with adequate donor hair were offered full coverage. Any patient with limited donor supply and extensive hair loss who asks for full coverage should be rejected because FU extraction should be limited to 25% of the donor FU and overharvesting should be avoided to avoid permanent damage of the donor area with resultant donor thinning and patchy hair loss (28, 29). Oedema of the forehead and or eyelid in the first week was a common consequence after hair transplantation in the first 115 patients. In an attempt to decrease postoperative oedema, in the last 156 cases, 40 mg of Triamcinolone was added to the LA solution in

addition to the usual postoperative instruction about head elevation and applying a cold gel pad to the forehead and donor area, which led to a dramatic reduction of the incidence of postoperative oedema, from 40% to 9% (Table 1) with highly significant P-value. Therefore; we can conclude that post-operative head elevation with the application of a cold gel pad alone was an ineffective way to prevent postoperative oedema, while the addition of 40 mg Triamcinolone to the LA solution was highly effective and we recommend it. Adding steroids to the tumescent solution was first recommended by Neil Dwyer for craniofacial surgeries. this study was on 20 cases of remodeling craniofacial surgery and concluded that the formula can decrease the incidence of postoperative periorbital oedema (30). Our findings reinforce the findings of Neil Dwyer. In another study Abbasi G. et al found that the addition of steroid to the tumescent solution was the most effective way to prevent postoperative oedema, However, physical methods and oral steroid was ineffective (31). Platelet-rich plasma (PRP) therapy is a relatively new appealing approach to tissue regeneration to promote healing in maxillofacial surgery, periodontal surgery, orthopedic, burns, cosmetic, and plastic surgery and more recently for its role in treating acne scar, fat grafting, and AGA (32, 33). The rate of the highly satisfied patients was increased from 64.5% to 83.7% with a P-value of 0.026 which was statistically significant (Table 2). PRP is rich in many growth factors and proteins. It is very rich in platelet-derived growth factor (PDGF), epidermal growth factor (EGF), transforming growth factor (TGF), fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF), and various pro and anti-inflammatory cytokines (34, 35). Growth factors in PRP promote hair regrowth by binding to their respective receptors expressed by stem cells of the hair follicle bulge region and associated tissues. Upon ligand binding, stem cells induce the proliferative phase of the hair follicle, producing the anagen follicular unit and facilitating hair regrowth (1, 36). Hair transplantation is a relatively safe surgery and is associated with very few complications, however, it can seriously impact the cosmetic and psychological outcome for the patients (24).

To avoid complications, the surgeon and the staff should be aware of possible complications and have a

prevention plan, and their management. Edema is not a complication per se, but more of a surgical consequence (31). As mentioned above, we successfully reduced the incidence of postoperative oedema by the addition of 40 mg Triamcinolone to the LA solution. Systemic complications were not seen in our study apart from transient hypotension in four cases that responded to lowering down the head and leg elevation. Wound infection was not reported in our patients. This could be attributed to our strict adherence to sterile precautions, preoperative shampooing with chlorhexidine gluconate, prophylactic antibiotic, excluding patients with a medical disease like diabetes, and good scalp vascularity. Farjio N. reported a 1% incidence of wound infection (37). Recipient site effluvium was seen in 9 (3.3%) patients, however; donor hair effluvium was seen in 11 (4.1%) patients as a diffuse donor effluvium after 3-6 weeks. The patients were reassured that it is a temporary phenomenon and Minoxidil spray was prescribed. Full recovery was seen after 3-4 months. Donor site effluvium was more common with overharvesting in the FUE method (28).

Folliculitis in the recipient area was seen in 20 (7.4%) patients after 2-3 months who were treated successfully with topical mupirocin and warm compresses.

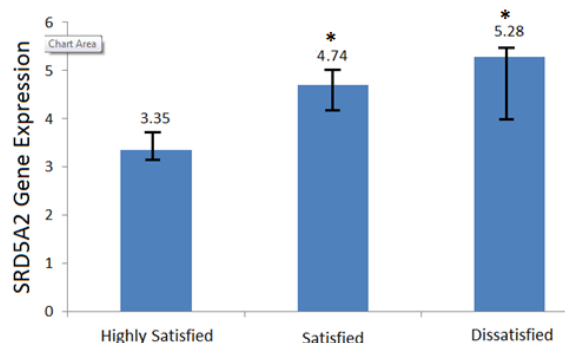
According to reports, the incidence of folliculitis after hair transplantation is 1.1-20% (38). In the first few days, 13 patients (4.8%) developed scabs in the receiving area. After successful treatment, an emollient was used to soften the scabs for 60 minutes and then gently cleaned and applied wet compresses. A few small slow-growing cysts around transplanted hair follicles were seen in 8 (3%) patients, treated successfully with incising the cysts and expelling their contents followed by wet compresses. These cysts were because of small grafts slipping under the skin (39, 40).

Genetic evaluation results showed that the expression of the SRD5A2 gene in dissatisfied and satisfied patients is significantly higher than highly satisfied ones. It means that in addition to affecting baldness, this gene also significantly affects the response to hair transplants. The SRD5A2 gene provides instructions for making steroid 5-alpha reductase 2 (18). The 5-alpha reductase-2 converts testosterone to dihydrotestosterone (DHT) in the

developing reproductive tissues, and DHT is the leading cause of androgenetic alopecia (14, 17).



**Figure 8.** The result without using three postoperative PRP sessions A: Preoperative. B: One year postoperatively. C-H: shows result of hair transplantation with three sessions of PRP at 2<sup>nd</sup>, 4<sup>th</sup>, and 6<sup>th</sup> months post operatively, leading to excellent natural result with denser, thicker and shiny hair. I: Invisible donor scar due to limiting our extraction rate to 25% of FU.



**Figure 9.** The SRD5A2 gene expression in highly satisfied, satisfied, and dissatisfied patients for hair transplantation

## Conclusion

Successful transplantation needs the adequate experience of the surgeon and staff, adhering to sterile precautions, and proper patient selection. Adding 40 mg Triamcinolone to the LA solution was highly effective in reducing postoperative oedema. Three sessions of PRP at 2<sup>nd</sup>, 4<sup>th</sup>, and 6<sup>th</sup> months post-operatively resulted in an increased patient satisfaction rate with better hair density and thickness. Also, the current study showed that the SRD5A2 gene expression had an important role in the success of hair transplantation. The increased expression of this gene could reduce the response to hair transplantation.

### Declaration of patient consent

We certify that we obtained written patient consent forms. In the form the patients gave their consent for their images to be reported in the journal. The patients understand that their names will not be published and every effort will be made to conceal their identity, but anonymity cannot be guaranteed.

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### Conflicts of interest

No conflicts of interest.

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