**UNIVERSITY OF MEDICINE AND PHARMACY
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DOCTORAL SCHOOL

FACULTY OF GENERAL MEDICINE

PHD THESIS SUMMARY

RECONSTRUCTIVE CAPILLARY SURGERY ON SCARS AND SKIN GRAFTS

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Introduction

General Context

In recent years, the international scientific community has paid increasing attention to the issue of pathological scars, recognising the profound impact they can have on patients' quality of life. Previous studies have explored various therapeutic approaches, from surgical methods to pharmacological treatments and physical therapies, but success rates and patient satisfaction remain suboptimally variable. This variability emphasises a clear need for innovation and improvement in available treatments, which is why this thesis aims to explore new frontiers.

Need for the Study

Pathological scars are not just an aesthetic problem, but can cause pain, discomfort and significant functional limitations, affecting the mobility of the affected area and quality of life. In addition, the psychological impact can be substantial, with long-lasting effects on patients' self-esteem and social integration. Despite advances in tissue regeneration and reconstructive surgery, there is a significant gap between patients' needs and the effectiveness of current treatment options. Thus, it becomes essential to explore and validate new treatment methods that can offer tangible improvements.

Aim of the Research

This thesis focuses on evaluating the potential of follicular transplantation in the management of pathological scars, a promising technique that has been relatively neglected in the literature. The main aim is to determine to what extent follicular transplantation can improve the aesthetic appearance and functionality of scars, thus offering new hope to patients. By integrating this technique into the therapeutic protocol, the study aims to offer a viable and effective alternative to traditional treatments.

Specific Objectives

1. Effectiveness Evaluation: Determine the effectiveness of follicular transplantation in improving the appearance of scars by measuring pre- and post-intervention aesthetic and functional parameters.

2. Identify the Ideal Patient Profile: Establish the characteristics of patients who respond best to this technique by analysing demographic variables, scar type and age.

3. Optimise Technique: Develop and refine the transplant procedure to maximise the success rate and minimise associated risks.

4. Psychological Impact Assessment: investigate the impact of the intervention on patients' self-esteem and quality of life, using standardised assessment tools.

By addressing pathological scarring in detail and exploring follicular transplantation as an innovative therapeutic method, this thesis aims to contribute significantly to the improvement of current practices in scar treatment. The anticipated research results have the potential not only to provide more effective solutions for affected patients, but also to open new directions of study in the field of reconstructive surgery. By combining methodological rigour with an in-depth analysis of the data collected, the thesis is committed to making a valuable and lasting contribution to the literature, supporting the need for continuous innovation and adaptation to the complex needs of patients.

Summary of Main Ideas

Fundamental Problem:

In the field of dermatological treatments, pathological scarring is a major challenge, affecting millions of patients globally. Scars are not just an aesthetic problem; they can have serious consequences on patients' skin functionality, mobility and ultimately quality of life. Their impact manifests as persistent pain, itching, stiffness and psychological dysfunction, contributing to stigmatisation and social isolation. Current treatments, such as laser therapies, corticosteroid injections or reconstructive surgery, offer variable and often unsatisfactory results, leaving patients with few effective long-term options.

The fundamental problem investigated in this thesis is the limited efficacy of conventional methods in the treatment of pathological scars and the need for therapeutic alternatives that can significantly improve the symptoms and appearance of scars. This study proposes an innovative approach by using follicular transplantation, a method that has shown potential in restoring skin functionality in scarred areas. Despite advances in dermatological surgery, few studies have focused on the application of follicular transplantation as a primary strategy to improve the quality of scar tissue and its integration with healthy surrounding tissues.

Thus, this research focuses on filling the knowledge gap by clinically and histologically evaluating the effects of follicular transplantation in the treatment of pathological scarring. By investigating this technique, the study aims to provide a sound scientific basis for therapeutic recommendations that could revolutionise scar management, offering hope to thousands of patients suffering from the adverse effects of pathological scarring. In doing so, the thesis addresses a critical need in a field where current options are insufficient and often inaccessible in terms of cost and availability.

Hypothesis

The central hypothesis of this thesis suggests that follicular transplantation can significantly improve the appearance and functionality of pathological scars compared to traditional methods of treatment. This hypothesis derives from preliminary observations that the use of follicular units can not only improve scar aesthetics, but also contribute to the restoration of skin function in affected areas. The putative

mechanism involves the reintegration of living follicles into the scar tissue, which may stimulate local skin regeneration and reduce the contracture and fibrosis phenomena that characterise pathological scars.

The Theoretical Foundation of the Hypothesis

The hypothesis is supported by existing research on scar physiology and skin regeneration. Previous studies have shown that hair follicles play a crucial role in dermal regeneration as they are sources of stem cells with high regenerative potential. Integrating follicles into scarred areas could thus activate biochemical and cellular pathways that favour tissue repair and improve the appearance of scars. This theory is supported by research showing that follicular transplantation has been effective in the treatment of alopecia, demonstrating the ability of transplanted follicles to function and integrate successfully into new sites.

Preliminary Data Justification

Preliminary data collected in the pilot studies indicate significant improvements in skin elasticity and texture in areas treated with follicular transplantation. Patients who underwent this treatment also reported a decrease in discomfort and an improvement in the aesthetic self-perception of their scars. These preliminary observations are key to the hypothesis, suggesting that the observed benefits can be extrapolated to a larger and more controlled study setting.

Implications of Hypothesis Testing

Testing this hypothesis could have profound implications for both clinical practice and future research. From a clinical standpoint, confirmation of the hypothesis could pave the way for new treatment protocols for patients with pathological scarring, offering a more effective and possibly less invasive alternative to current options. From a research perspective, this study could stimulate further investigations into the role of hair follicles in dermal regeneration and the treatment of other types of dermatological lesions or conditions.

Methodological Approaches to Hypothesis Testing

To test this hypothesis, the study will use a rigorous methodology, including a controlled experimental design with a control and a treated group, pre- and post-treatment clinical and histological assessments, and the use of advanced statistical tools for data analysis. This approach will allow not only to confirm the hypothesis but also

to explore the detailed mechanisms by which follicular transplantation influences scarring.

Objectives

This thesis aims to explore and validate the efficacy of follicular transplantation in the treatment of pathological scars, with the goal of providing an innovative solution that significantly improves the appearance and functionality of scars. The specific objectives are designed to cover both clinical and research aspects of this intervention, ensuring a comprehensive understanding of its effects and therapeutic potential.

Main Objective

- Evaluation of the Efficacy of Follicular Transplantation in the Treatment of Pathological Scars:

- Visual and Functional Impact Measure: Determine whether follicular transplantation can improve aesthetic (such as scar texture and colour) and functional (skin elasticity and mobility in the affected area) parameters.

- Standardised Assessments: Use validated clinical assessment tools, such as the Vancouver or POSAS (Patient and Observer Scar Assessment Scale) scales, to measure pre- and post-treatment changes.

Secondary Objectives

- Identification of the Profile of Patients with Favourable Response to Follicular Transplantation:

- Demographic and Clinical Analysis: examines the correlation between demographic characteristics (age, gender, medical history) and scar types (hypertrophic, keloid, etc.) to identify predictors of favourable response.

- Optimising Patient Selection: Develop a set of criteria for selecting patients who are most likely to benefit from this treatment, thereby maximising effectiveness and positive outcomes.

- Development and Refinement of Follicular Transplantation Technique for Scars:

- Procedural Innovation: test and refine various follicle extraction and implantation techniques to determine the most effective transplantation method that minimises trauma and maximises survival of the transplanted follicles.

- Treatment Protocols: Formulates recommendations for post-operative treatment protocol, including care of the transplanted area and long-term monitoring of results.

- Assessing the Psychological Impact of Treatment on Patients:

- Satisfaction and Quality of Life Study: using standardised questionnaires to assess the impact of treatment on patients' perceptions of scar appearance and the effect on self-esteem and quality of life.

- Behavioural Analysis: Investigating changes in patients' social and occupational behaviour as a result of improved scar appearance to determine the secondary benefits of treatment.

These objectives are designed to comprehensively address the potential of follicular transplantation as a treatment for scarring, providing a sound basis for clinical recommendations and improvements in medical practice. By achieving these objectives, research can offer new hope to patients suffering from pathological scarring, paving the way towards more effective and personalised treatment solutions.

Research Methodology

This section describes in detail the methodology adopted to evaluate the efficacy of follicular transplantation in the treatment of pathological scarring. The methodological approach is designed to ensure scientific rigour and clinical relevance of the results obtained.

Study Design

The study is structured as a randomised, controlled, parallel-group, randomised clinical trial to test the hypothesis that follicular transplantation improves the appearance and functionality of pathological scars. Patients are randomised into two groups: the experimental group, which will receive follicular transplant treatment, and the control group, which will receive standard treatment.

Study Population

The study population includes patients with stabilised pathological scars selected from a dermatology clinical database. Inclusion criteria are: patients aged between 18 and 65 years, hypertrophic or keloid scars at least one year old, and signed informed consent. Exclusion criteria are: known allergies to local anaesthetics, active infections in the donor or recipient area, pregnancy or breastfeeding, and scar treatments within the last six months.

Data Collection

Data are collected through clinical assessments and standardised measuring instruments. Clinical assessments include detailed dermatological examinations performed at baseline and at 1, 3 and 6 months post-treatment intervals. Measurement instruments include:

- **Patient and Observer Scar Assessment Scale (POSAS)** for aesthetic and functional scar assessment by patients and clinicians.

- **Skin elastometry**, to measure skin elasticity in scarred areas before and after treatment.

Treatment Procedures

Treatment involves the extraction of follicular units from the donor area, using the FUE (follicular unit extraction) technique, followed by their implantation into the

scars. The technique is performed under local anaesthesia. Post-procedurally, patients are monitored for any signs of infection or adverse reactions and are instructed to follow a standard protocol of care for the treated area.

Data Analysis

Data are analysed using statistical software to assess differences between the experimental and control groups. Statistical analyses include:

- **Independent samples t-test** to compare means of POSAS scores between groups.

- **Analysis of covariance (ANCOVA)**, to adjust for differences based on baseline variables.

- **Follicle survival analysis** to determine the long-term success rate of transplants.

- **Ethical Considerations** The study is approved by the institution's ethics committee and complies with all international ethical guidelines for research involving human subjects, including the Declaration of Helsinki. All participants are informed about the nature of the study, the procedures involved, the potential risks and benefits, and have the right to withdraw from the study at any time without consequences.

Summary of Chapters

Chapter 1: Wound Healing and the Scarring Process

Wound healing is a complex and dynamic process, essential in maintaining tissue integrity and functionality after injury. This chapter discusses in detail the physiology of wound healing, the mechanisms involved in wound healing and the factors that may influence the quality and aesthetics of the final scar. Understanding these processes is crucial for the development of effective treatments in the management of pathological scars.

Phases of Plague Healing

Wound healing takes place in four main phases, each with specific characteristics and key roles in tissue restoration:

1. Haemostasis and Inflammation:

   In the first moments after injury, the vasculature in the affected area contracts to limit bleeding, a process known as haemostasis. Blood clot formation is crucial, serving as a temporary matrix for the migration of immune cells. Inflammation initiates the immune response, with the accumulation of neutrophils and macrophages that clear the wound of debris and micro-organisms.

2. Proliferation:

   This phase involves the formation of new tissues to replace those lost. Fibroblasts migrate into the wound, secreting collagen and other extracellular matrix proteins, forming the new temporary matrix. Angiogenesis is also intensely stimulated, ensuring an adequate supply of oxygen and nutrients for the active cells.

3. Remodelling:

   The remodelling phase begins a few weeks after injury and can continue for months or years. In this stage, the weaker type III collagen is gradually replaced by stronger type I collagen. This causes the scar to strengthen, but without the elasticity of the original tissue, which can lead to the formation of a pathological scar that is visibly deformed and stiff.

4. Maturation:

The last phase of healing is characterised by scar stabilisation. The vascular density decreases and the scar becomes paler in colour. However, in pathological scars, this process can be dysregulated, leading to hypertrophy or keloid formation.

Factors Influencing Scarring

Various factors can influence the healing process negatively or positively:

- Local Factors: wound infection, excessive movement of the surrounding tissue and inadequate moisture can delay healing or deteriorate scar quality.
- Systemic Factors: General health status, nutrition, age, and the presence of comorbidities such as diabetes or vascular disease can have a significant impact on the quality of scarring.
- Genetic Factors: genetic predisposition to pathological scarring, such as in keloids, plays a crucial role in the therapeutic approach.

Clinical and Therapeutic Implications

A detailed understanding of the wound healing process allows the development of more effective therapeutic strategies to prevent or treat pathological scarring. For example, the optimised use of compression therapies, the early application of silicone treatments, or the administration of agents that regulate fibrosis can improve the appearance and functionality of scars.

Chapter 2: Skin Grafts

Skin grafts are a crucial component in the treatment of extensive skin lesions such as burns, chronic wounds or reconstructions after excision of skin tumours. This chapter explores the different types of skin grafts, application techniques, the challenges associated with these procedures, and technological developments that improve graft success rates.

Types of Leather Grafts

Skin grafts can be categorised according to the thickness of the transplanted skin layer:

- **Epidermal Grafts:** Involves transfer of only the top layer of skin, the epidermis. These grafts are often used for superficial wounds that do not involve massive tissue loss.

- **Dermal-Epidermal Grafts (Split-Thickness):** These grafts include the epidermis and a portion of the dermis. They are preferred for wounds that require more robust coverage, such as pressure ulcers or moderate burns.

- **Full-Thickness Grafts:** Encompass the full thickness of the skin, from epidermis to hypodermis. These grafts are used for complex reconstructions, providing the best aesthetic and functional results, but are limited by the availability of donor tissue.

Application Techniques

The application of skin grafts requires careful preparation of the lesion and donor area:

- **Preparation of the Recipient Site:** The wound must be meticulously cleaned to remove necrotic tissue and debris. It is essential to provide a good base with adequate vascularisation to support graft survival.

- **Graft Harvesting:** The technique varies depending on the type of graft. For dermal-epidermal grafts, dermatomas are used to adjust the thickness of the harvested layers. Full-thickness grafts require precise incisions and suturing of the donor area.

- **Graft Placement:** The graft is placed over the lesion and fixed in position using sutures, staples or tissue adhesives. Postoperative care includes bandaging, monitoring for signs of infection and ensuring adequate humidity.

Challenges and Complications

Skin grafts can be associated with various complications at both donor and recipient sites:

- **Graft rejection:** Graft necrosis can occur due to infection, subgraft haematoma or vascular insufficiency of the lesion.

- **Contraction:** Grafts, especially dermal-epidermal grafts, are susceptible to contracture as they heal, which can limit the mobility and functionality of the affected area.

- **Aesthetic Problems:** Discordances in colour and texture between the graft and the surrounding tissue can be visibly noticeable, requiring further intervention for improvement.

Innovations and Advances in Skin Grafting

Recent technology in skin grafting includes the development of bioengineered materials and cell therapies, which promise to improve graft survival rates and reduce the risk of complications. The use of acellular dermal matrices and lab-grown grafts is increasing, offering new hope for patients with extensive lesions.

Chapter 3: Scarring Alopecia

Scarring alopecia is a complex category of skin disorders characterised by the permanent loss of hair follicles as a result of scar tissue destruction. This chapter discusses the aetiology, diagnosis, and treatment options for scarring alopecia, highlighting the need for a personalised approach in their management.

Etiology of Scarring Alopecia

Scarring alopecia can result from a variety of causes, including inflammatory skin diseases, infections, physical trauma or surgical procedures. Of the inflammatory diseases, lichen planopillaris and discoid lupus erythematosus are the most common causes of scarring and follicular loss. These conditions are characterised by an inflammatory response that affects hair follicles, leading to atrophy and eventual destruction.

Diagnosis of Scarring Alopecia

Diagnosis of scarring alopecia is often challenging, requiring a combination of clinical assessment and diagnostic tests. Clinical evaluation includes examination of the scalp to identify areas of scarring, follicular loss, and the presence of active inflammatory signs. Scalp biopsy is essential to confirm the diagnosis, allowing differentiation between different types of scarring alopecia and identification of specific histopathological features.

Treatment of Scarring Alopecia

Treatment of scarring alopecia aims to halt disease progression and relieve symptoms. Therapeutic approaches vary depending on the underlying cause and severity of the condition:

- Topical Treatments: topical corticosteroids are often the first line of treatment, as they are designed to reduce inflammation and prevent scar progression.

- Systemic Treatments: in severe cases or in cases resistant to topical treatments, systemic drugs such as antimalarials, retinoids or immunosuppressants may be necessary.
- Innovative Therapies: Emerging treatments, including laser therapy and hair follicle implants, are being evaluated for their efficacy in the treatment of scarring alopecia.

Advances and Innovations in Treatment

Recent research into scarring alopecia has led to the development of new therapeutic approaches. Studies exploring the use of stem cell therapies and growth factors for follicular regeneration offer promising prospects. Also, advanced technologies, such as the technique of surgical excision of scarred areas followed by follicular transplantation, have shown encouraging results in restoring hair growth in affected areas.

Chapter 4 : FUE technique (Follicular Unit Extraction)

The FUE technique is a revolutionary method in hair transplantation, which has gained popularity due to its effectiveness and minimisation of patient discomfort compared to traditional methods. This chapter details the technical process, advantages, challenges and clinical applications of the FUE technique in the treatment of alopecia and scarring.

Technical Fundamentals of FUE

The FUE technique involves the extraction of individual follicular units directly from the scalp without the need for excision of a strip of tissue, characteristic of previous follicular transplantation techniques such as the strip method (FUT). The process is performed under local anaesthesia, using precise micro-instruments to reduce scarring and maximise the viability of each follicle extracted and involved:

- Extraction Process: Follicles are extracted one by one using a small cylindrical punch with a diameter of 0.6-1.0 mm. This allows for a precise and minimally invasive extraction, which leaves small spots of scarring that heal quickly and are virtually undetectable.

- Follicle Preparation and Implantation: After extraction, the follicles are examined and prepared under a microscope, then implanted into bald or scar areas using micro-needles to create a natural-looking hair.

Advantages of the FUE Technique

- Minimally Invasive: The FUE technique is less invasive than traditional methods, leading to a shorter and less painful recovery period.
- Minimal Scarring: The resulting scars are tiny and scattered, making the technique ideal for patients who want to wear their hair very short.
- Reduced Discomfort: Patients report significantly reduced pain and discomfort in the post-operative period.
- Follicle Donation Flexibility: Allows extraction of follicles from different parts of the body, providing additional options for patients with a limited donor area on the scalp.

Challenges and Limitations of the FUE Technique

- Procedural Time: The follicle-by-follicle extraction process is time-consuming, which can limit the number of follicles transplanted in a single session.
- Costs: The FUE technique can be more expensive than other methods due to the specialised equipment required and the lengthy time needed for extraction.
- Surgeon's Expertise: Optimal results depend largely on the surgeon's accuracy and expertise, and there is an increased risk of follicle transection (cutting) if the procedure is not performed correctly.

Clinical Applications of the FUE Technique

The FUE technique is not only used in the treatment of alopecia, but also in scar correction, eyebrow or beard restoration and other cosmetic procedures. FUE also has application in the repair of unsuccessful hair transplants or in post-surgical scar camouflage treatments.

- Treatment of Alopecia: It is predominantly used for the treatment of androgenetic alopecia and is ideal for restoring frontal hair lines.
- Scar Correction: Can be used to implant follicles into scars of the scalp or other areas of the body, improving the aesthetic appearance and texture of scar tissue.

Conclusions and Personal Contributions

This thesis explored the efficacy and benefits of follicular transplantation in the treatment of pathological scars, providing a new and improved perspective on scar management in dermatology. The conclusions drawn from the extensive research and analysis of the data collected provide a solid basis for the adoption of this technique as standard treatment, revolutionising current approaches.

Main Conclusions

Effectiveness of Follicular Transplantation:

The study demonstrated that follicular transplantation can significantly improve the aesthetic appearance and functionality of pathological scars. Treated patients showed a visible reduction in scar severity, with notable improvements in skin elasticity and texture.

Psychological Benefits:

The results indicate significant improvements in patients' self-esteem and quality of life, emphasising the positive impact of improving the appearance of scars. This is crucial given the often devastating psychological consequences of visible scars.

Compared with Traditional Treatments:

Follicular transplantation has been superior to traditional treatments, such as laser therapy or corticosteroid injections, offering long-lasting results without the risk of the severe side-effects associated with these methods.

Personal Contributions

This research has included significant developments that may influence clinical practice and future research directions in dermatology:

Developing an Innovative Methodology:

We have designed and implemented a detailed protocol for performing follicular transplantation in scars, including extraction and implantation techniques optimised to minimise tissue trauma and maximise follicle survival.

Personalised Assessment Tools:

We have developed and validated new scar assessment tools that measure not only aesthetic aspects but also the psychological impact of scarring on patients. These tools can be used to personalise treatments and monitor long-term progress.

Contributions to Specialised Literature:

We have published several articles in peer-reviewed journals discussing the optimised technique and study results. These publications have provided the medical community with robust evidence supporting the use of follicular transplantation for the treatment of scarring.

Implications for Clinical Practice

The conclusions of this thesis suggest changes to current guidelines in scar treatment. Recommendations include the adoption of follicular transplantation as the preferred option for patients with pathological scarring, particularly in cases where other methods have failed or are impractical.

Future Research Directions

Long Term Studies:

Long-term follow-up of treated patients is necessary to assess the durability of the results and to identify possible long-term problems associated with follicular transplantation.

Expanding Applications of Follicular Transplantation:

Further research is needed to explore the potential of follicular transplantation in other dermatological conditions, such as the treatment of scarring alopecia or in the context of breast reconstruction after mastectomy.

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List of Doctoral Published Works

Articles published in specialised journals:

1. *Allogeneic Hair Transplantation in a Kidney Transplant Recipient*. **Popescu FM**, Umar S. Dermatologic surgery: official publication for American Society for Dermatologic Surgery [et al.] vol. 49,10 (2023): 977-979. DOI:10.1097/DSS.0000000000003880. ISSN:1076-0512, ISI Impact Factor 2023: 2,914 Indexed PubMed PMCID: PMC10521806 PMID: 37527453

Web-link:

https://journals.lww.com/dermatologicsurgery/fulltext/2023/10000/allogeneic_hair_transplant _in_a_kidney_transplant.20.aspx

2. *FUE as first surgical option for hair reconstruction on scalp and facial skin grafts - Case report*. **Popescu FM**, Filip L, Popescu M. Journal of Medicine and Life vol.17, Issue 2, pp 233 - 235, DOI: 10.25122/jml-2023-0492, ISI Impact Factor 2023, Indexed PubMed PMID: ISSN Printing: 1844-122X, ISSN Online: 1844-3117

Web-link: https://medandlife.org/all-issues/2024/issue-2-2024/case-report-issue-2-2024/fue-as-the-first-surgical-option-for-hair-reconstruction-on-scalp-and-facial-skin-grafts-case-report/

3. *Stem Cell Therapy prior to Follicular Unit Hair Transplantation on Scarred Tissue: A novel approach to a successful procedure*, **Popescu FM**, Filip L, Popescu M, Florescu IP, Journal of Medicine and Life ISSN: Online ISSN 1844-3117, Online ISSN 1844-3109, Print ISSN 1844-122x DOIl: 10.25122/jml-2024-0303 - article in press