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Modern Strategies in Chronic Wound Management – Possibilities and Limitations

SUMMARY OF THE DOCTORAL THESIS

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Introduction

Chronic wounds represent a major public health concern, not only due to their increasing prevalence but, more importantly, because of their complex impact on both the patient and the healthcare system. These lesions, defined by their inability to progress through the normal physiological stages of healing, are frequently associated with chronic pain, an increased risk of infection, reduced mobility, and, consequently, a significant decline in quality of life. Furthermore, they generate considerable direct costs—recurrent hospitalizations, advanced wound dressings, and surgical interventions—as well as indirect costs related to loss of work capacity and the need for long-term care.

In Romania, the management of chronic wounds is characterized by marked heterogeneity, largely due to the absence of a unified national therapeutic protocol. Clinical practice varies significantly depending on the physician's individual experience, the specialty involved, and access to modern treatment resources. This variability inevitably leads to inconsistent and, at times, suboptimal patient outcomes. At the same time, limited access to advanced therapies, such as regenerative approaches or modern wound care technologies, further accentuates disparities between medical centers and between urban and rural settings.

In this context, the need for a standardized, multidisciplinary, and evidence-based approach becomes evident. Such a model would not only optimize clinical outcomes but also enable a more efficient allocation of resources, facilitating the integration of modern therapies and the development of guidelines tailored to the realities of the Romanian healthcare system.

The choice of this research topic is grounded in direct clinical experience in the management of chronic wounds, where the limitations of conventional treatments frequently become apparent, particularly in complex cases involving associated comorbidities or delayed therapeutic response. Repeated exposure to unpredictable clinical evolution, the necessity for extensive surgical interventions, and the substantial impact on patients' quality of life have underscored the need to explore more effective and less invasive therapeutic alternatives.

Within this framework, interest in regenerative therapies has emerged as a natural extension of clinical practice, oriented toward stimulating the body's intrinsic healing mechanisms. Platelet-rich plasma (PRP) and autologous fat grafting represent two of the most promising options, due to their high content of growth factors, cytokines and cells with regenerative potential. These therapies do not act merely at a symptomatic level, but rather

directly target the pathophysiology of chronic wounds, promoting angiogenesis, cellular proliferation, and tissue remodeling.

Data from the specialized literature, supported by our own clinical observations, indicate that the use of these methods can accelerate the epithelialization process, reduce the size of tissue defects, and, in certain situations, avoid the need for major surgical procedures such as complex flaps or amputations. Moreover, the combination of PRP and autologous fat grafting appears to have a synergistic effect, particularly in deep or ischemic wounds, where tissue regeneration is severely compromised.

Thus, the chosen topic not only reflects a current direction in research but also addresses a real need in medical practice, with the potential to contribute to the optimization of therapeutic strategies and the improvement of prognosis in patients with chronic wounds.

The novelty of the research lies both in the integration of regenerative therapies into the management of chronic wounds and in the evaluation of the practices and perceptions of physicians in Romania, highlighting the interest in these methods, as well as the limitations related to infrastructure and training.

The study aligns with international trends in regenerative medicine and reconstructive surgery, while emphasizing the lack of clinically relevant data for the Eastern European population, particularly regarding the efficacy of PRP and autologous grafts.

The working hypothesis supports that autologous regenerative therapies, applied in an individualized manner, can reduce healing time, complications, and the risk of amputation compared to conventional treatments.

The research methodology was designed to integrate both the clinical and practical dimensions of chronic wound management. The prospective component included 35 patients with chronic wounds of varied etiologies, treated with PRP, with or without autologous fat grafting and, in certain cases, with dermoepidermal grafting. Patients were followed dynamically, using objective parameters such as wound surface area, epithelialization rate, signs of local infection, and the need for antibiotic therapy or additional surgical interventions. In parallel, the sociological component included a questionnaire administered to 240 physicians from relevant specialties, in order to evaluate current practices, the degree of use of regenerative therapies, and the existing barriers to their implementation.

Data analysis was performed using appropriate statistical methods, including significance and correlation tests, and the results were interpreted in the context of the existing literature. This mixed-methods approach allowed not only the evaluation of the clinical efficacy of regenerative therapies but also an understanding of how they are perceived and integrated into medical practice in Romania.

The results of the clinical study are practically relevant: a complete healing rate of 45.7% and an average reduction in wound surface area of over 90% indicate a significant therapeutic effect, particularly in the context of difficult cases with chronic evolution. Combined therapy using PRP and autologous fat grafting demonstrated superior efficacy compared to PRP monotherapy, suggesting a synergistic effect between growth factors and the regenerative cellular component of adipose tissue, especially in deep or ischemic wounds.

Regarding dermoepidermal grafting, the results did not demonstrate a significant additional benefit when combined with PRP, raising questions about the optimal indications and timing of its integration into the therapeutic algorithm. Another important aspect is the favorable effect of PRP on infection control, through the reduction of infection incidence and, consequently, the need for systemic antibiotic therapy, which may have relevant implications in the current context of bacterial resistance.

Overall, the results support the use of regenerative therapies as viable and effective options in the management of chronic wounds, particularly when integrated into a personalized and multidisciplinary therapeutic plan. These findings contribute to strengthening the existing body of evidence and provide arguments for the inclusion of these methods in standardized treatment protocols.

The study highlights the need for protocol standardization and the development of infrastructure for regenerative therapies, in the context of limitations such as the relatively small sample size, case heterogeneity, and the lack of economic analyses. Future directions include multicenter studies and the integration of these therapies into national guidelines.

General part

Chapter 1 - Chronic wounds – current perspectives in epidemiology, pathogenesis, and management

1.1. Definition, epidemiology and socioeconomic impact

Chronic wounds are classically defined as lesions that fail to progress through the normal stages of healing within a time frame considered appropriate. Although variable temporal thresholds have been proposed in the literature—from 4 weeks to over 3 months—there is no clear consensus regarding the duration that defines chronicity. This lack of conceptual uniformity represents more than a theoretical issue; it has direct implications for clinical practice and research, limiting the comparability of studies and the standardization of therapeutic approaches. Furthermore, the heterogeneity of definitions is amplified by the etiological diversity of chronic wounds and by the different methods used to assess prevalence and incidence, making it difficult to accurately estimate the global impact of this pathology. Therefore, epidemiological data must be interpreted with caution in light of these methodological limitations [1,2].

From an epidemiological perspective, chronic wounds affect approximately 4% of the general population worldwide, with a significantly higher incidence among elderly individuals and patients with comorbidities, particularly diabetes mellitus, chronic venous insufficiency, or peripheral arterial disease. The most common forms include pressure ulcers, venous ulcers, neuropathic ulcers (especially diabetic foot ulcers), and ischemic wounds. In diabetic patients, the lifetime risk of developing a foot ulcer is estimated at approximately 25%, and its clinical relevance is underscored by the fact that the majority of non-traumatic lower limb amputations are preceded by such lesions. These data reflect not only the high prevalence of the condition but also the severity of its associated complications [3].

The economic impact of chronic wounds is substantial and often underestimated. Direct costs include recurrent hospitalizations, advanced wound dressings, antibiotic therapy, and surgical interventions, while indirect costs are generated by disability, loss of work capacity, and reduced quality of life. Consistently, the treatment of a chronic wound is 2–4 times more expensive than that of an acute wound. Internationally, the financial burden is

significant: in the United States, millions of patients are affected annually, with costs exceeding tens of billions of dollars, while in Europe and Australia estimates indicate expenditures in the range of billions. In the context of an aging population and the increasing prevalence of chronic diseases, these costs are expected to rise in the absence of effective and cost-efficient therapeutic strategies [4,5].

1.2. Classification of chronic wounds

Chronic wounds can be classified, in a simplified manner with clinical utility, according to their etiology. The most common are venous ulcers of the lower limb, accounting for 60–80% of leg ulcers, caused by venous insufficiency and characterized by irregular margins, supramalleolar location, edema, and hyperpigmentation. Diabetic foot ulcers occur in the context of peripheral neuropathy and vascular impairment, and are frequently located on the plantar surface. Pressure injuries are caused by prolonged compression or shear forces over bony prominences and are staged from superficial erythema to deep tissue loss. Arterial ulcers, caused by peripheral arterial disease, are typically painful, deep, and distally located, at the level of the toes or foot [6].

Etiological classification essentially includes neuropathic/diabetic wounds, venous ulcers, ischemic wounds, and pressure injuries, to which post-traumatic, oncological, or postsurgical wounds that fail to progress toward healing within a physiological timeframe are added. This etiological approach is essential for guiding therapeutic management and for the individualization of treatment [7].

1.3. Pathogenic mechanisms involved in wound chronicity

Wound chronicity occurs when the physiological healing process is disrupted, and the lesion remains arrested in the inflammatory phase, failing to progress toward proliferation and tissue remodeling. This phenomenon is not driven by a single mechanism, but rather by a set of interdependent factors that create a true local vicious cycle. Persistent inflammation plays a central role, being characterized by an excess of neutrophils and activated macrophages, which release increased amounts of proinflammatory cytokines (such as TNF-α and IL-1β) and proteases. A key element is the impaired transition of macrophages from the

proinflammatory M1 phenotype to the M2 phenotype, which is involved in tissue repair. In the absence of this transition, the healing process remains incomplete and ineffective [8,9].

Another major factor involved in maintaining chronicity is the increased bacterial load, particularly through biofilm formation. This represents an organized structure of microorganisms that adhere to the wound surface and become resistant to antibiotics and to the host's immune mechanisms. Biofilm sustains inflammation at a constant level and promotes recurrent infections, even after apparently favorable periods of evolution. In parallel, angiogenesis is impaired, and the availability of essential growth factors (VEGF, PDGF, TGF-β) is reduced, limiting neovascularization and tissue regeneration. This imbalance is further aggravated by oxidative stress and mitochondrial dysfunction, frequently encountered in conditions such as hyperglycemia or ischemia, where the excess of reactive oxygen species (ROS) induces additional cellular damage and accelerates tissue senescence [10].

Additionally, in chronic wounds there is a significant imbalance between matrix metalloproteinases (MMPs) and their inhibitors (TIMPs), leading to accelerated degradation of collagen and the extracellular matrix. This degradation prevents the formation of a stable scaffold for cellular migration and the development of high-quality granulation tissue, while simultaneously consuming growth factors before they can exert their biological effects. Consequently, the re-epithelialization process is delayed or incomplete, and the wound remains in a state of biological stagnation [11].

1.4. Systemic aggravating factors and associated comorbidities

In addition to local factors, the evolution of chronic wounds is profoundly influenced by systemic factors and comorbidities. Diabetes mellitus is one of the most significant risk factors, through the association of peripheral neuropathy, microangiopathy, and immune dysfunction. Mechanical factors, such as prolonged pressure, shear forces, or repetitive microtrauma, play an essential role in pressure injuries and diabetic foot, where the lack of adequate offloading perpetuates the lesion. Chronic venous insufficiency contributes through stasis, venous hypertension, and edema, promoting local inflammation and reducing tissue oxygenation [12].

Obesity and malnutrition are other relevant systemic factors, although often underestimated. Obesity exacerbates edema and impairs tissue perfusion, while malnutrition, through protein and micronutrient deficiencies (vitamins C, A, D, zinc), compromises collagen synthesis, cellular proliferation, and immune response. Anemia further contributes by reducing oxygen-carrying capacity, thereby aggravating tissue hypoxia. In addition, immunosuppressive therapies, chemotherapy, or radiotherapy may inhibit cellular proliferation, angiogenesis, and defense mechanisms, increasing the risk of necrosis and infection [13].

Overall, wound chronicity results from the complex interaction between local and systemic factors, which hinder the normal progression of healing. Understanding these mechanisms is essential for the development of effective therapeutic strategies, aimed not only at local wound treatment but also at correcting systemic contributing factors [14].

1.5. Clinical evaluation and current principles of chronic wound management

Accurate and systematic evaluation of a chronic wound is essential for establishing treatment, monitoring progression, and estimating prognosis. In modern practice, this is based on a combination of standardized clinical parameters, validated scoring systems, and imaging methods, which allow an objective assessment of healing and early identification of factors that may hinder progress. However, evaluation remains insufficiently standardized, with significant differences between centers and evaluators, limiting data comparability and introducing a degree of subjectivity in the interpretation of results [15].

Key evaluation parameters include wound size (length, width, depth), characteristics of exudate, the appearance of perilesional skin, the proportion of granulation tissue versus necrosis, the dynamics of wound edges, and pain intensity. These indicators provide direct information about the stage of healing and may signal complications such as infection or ischemia. For a more structured assessment, validated clinical scores are used, such as PUSH and BWAT, which quantify wound progression over time, as well as the TIME framework, which guides management through the assessment of tissue, infection/inflammation, moisture, and wound edges [16,17].

Evaluation is complemented by imaging techniques and modern digital technologies, such as standardized sequential photography, thermography for detecting inflammation and

ischemia, and bacterial fluorescence for identifying biofilm. Additionally, dedicated software applications allow precise measurement of wound surface area and monitoring of progression. Overall, rigorous and standardized assessment remains a key element in optimizing chronic wound management [18].

In chronic wounds, the infectious component is often difficult to distinguish from baseline inflammation or the presence of biofilm, frequently leading either to overtreatment of colonization or underdiagnosis of true infections. Therefore, clinical evaluation remains essential, while microbiological cultures and biomarkers should be regarded as complementary tools for confirmation and stratification, rather than substitutes for clinical examination. Colonization is nearly universal and does not justify systemic antibiotic therapy, whereas biofilm can sustain inflammation and delay healing, primarily requiring local treatment. In contrast, true infection involves tissue invasion and manifests through local and/or systemic clinical signs, in which case antibiotic therapy becomes necessary [19].

The relevance of microbiological cultures depends on the clinical context and the sampling method. They are particularly useful in the presence of signs suggestive of infection (purulent exudate, progressive erythema, newly developed pain, stagnation of healing, or systemic signs). Proper sampling, ideally after wound cleansing and debridement, is essential for result accuracy, with the Levine technique being preferable to superficial swabbing. In cases of suspected deep infection or therapeutic failure, aspirates or tissue biopsy provide more relevant information. However, biofilm may influence results, leading either to falsely reassuring findings or to bacterial isolation without direct clinical relevance [20].

Serum biomarkers, such as CRP and procalcitonin, are useful in assessing systemic inflammatory response and monitoring evolution, but have limitations in diagnosing local infection. CRP is sensitive but nonspecific, while procalcitonin is more indicative of systemic bacterial infections. Other parameters, such as leukocyte count or the neutrophil-to-lymphocyte ratio, may support the suspicion of infection but are influenced by numerous factors. Overall, the interpretation of cultures and biomarkers must be integrated into the clinical context to avoid unnecessary antibiotic use and to guide appropriate treatment [21].

The treatment of chronic wounds requires a structured, stepwise, and individualized approach, based on comprehensive evaluation of both the patient and the local wound characteristics. The therapeutic strategy must be adapted to etiology, comorbidities, and

vascular and infectious status, with a multidisciplinary approach being essential. Control of underlying conditions, such as diabetes, venous insufficiency, or malnutrition, represents a central component, as these directly influence healing capacity [22].

Another important pillar is the optimization of tissue perfusion, through vascular assessment and, when necessary, surgical or endovascular revascularization. In parallel, the prevention of stagnation and recurrence of lesions, particularly in venous ulcers, is achieved through appropriate compression therapy [23]. Local wound control involves regular debridement to remove necrotic tissue and biofilm, followed by the use of tailored dressings, including modern active dressings that create a favorable environment for healing [24].

Advanced technologies, such as negative pressure wound therapy, are useful in complex wounds, promoting granulation tissue formation and reducing bacterial load. In refractory cases, regenerative therapies, such as PRP or autologous fat grafting, offer a promising alternative by targeting the biological mechanisms of healing. Overall, treatment success depends on the integration of these methods into a personalized plan that is continuously adapted to the clinical evolution [25].

Chapter 2. Modern strategies in the treatment of chronic wounds – regenerative therapies and their limitations

2.1. Transition from conventional treatments to regenerative therapies

Conventional treatment of chronic wounds, based on debridement, dressings, antibiotic therapy, and the control of comorbidities, is often insufficient to achieve durable healing. In this context, regenerative therapies have gained increasing interest over the past two decades, as they directly target the biological mechanisms involved in impaired healing. These therapies act by providing growth factors, regenerative cells, and components of the extracellular matrix, thereby stimulating angiogenesis, cellular proliferation, and tissue regeneration [26].

2.2. Platelet-rich plasma (PRP)

Chronic wounds are characterized by dysfunctional microenvironment, dominated by persistent inflammation, increased proteolytic activity, and a deficiency of growth factors, all of which impair normal healing. An excess of neutrophils and proinflammatory macrophages leads to the release of cytokines and enzymes (MMPs) that degrade the extracellular matrix and consume essential growth factors (PDGF, VEGF, TGF-β). In parallel, oxidative stress, hypoxia, and recurrent infections further aggravate the local imbalance, promoting chronicity and cellular senescence. In this context, active intervention is required to modify the wound microenvironment and restore conditions favorable for healing [26].

Platelet-rich plasma (PRP) represents such an intervention, based on the concentrated use of autologous platelets, which are rich in growth factors and bioactive mediators. Platelets contain alpha and dense granules that release a wide range of factors involved in regeneration—PDGF, TGF-β, VEGF, EGF, FGF—with roles in stimulating angiogenesis, cellular proliferation, and collagen synthesis. In addition to these factors, PRP also contains cytokines, chemokines, and adhesion proteins that contribute to tissue remodeling, regulation of inflammation, and stabilization of local architecture. Thus, the effect of PRP is not singular, but rather the result of a complex biological action on the entire wound microenvironment [27].

PRP preparation involves the collection of autologous blood followed by centrifugation to obtain an increased platelet concentration, ideally exceeding 1 million/μL. There are numerous preparation systems, with significant variations in the final composition (platelet and leukocyte content, activation methods), which influence clinical outcomes. The lack of standardization represents one of the main limitations of this therapy, as PRP products of variable quality may generate different therapeutic responses. Therefore, tailoring PRP composition to wound characteristics and ensuring quality control are essential for achieving efficacy [28,29].

From a clinical perspective, current evidence supports a promising role for PRP in the treatment of chronic wounds, particularly in diabetic foot ulcers. Studies and meta-analyses demonstrate increased healing rates and reduced time to complete wound closure, in some cases even with a decreased risk of amputation. Similar benefits have also been reported in venous ulcers, pressure injuries, and other types of chronic wounds, with PRP being considered a safe method with minimal adverse effects [30].

However, the quality of evidence remains heterogeneous due to variations in preparation methods, platelet concentration, application techniques, and the types of wounds studied. This lack of standardization limits comparability of results and hinders the universal integration of PRP into clinical guidelines. Consequently, although PRP represents a promising and biologically grounded therapeutic option, further well-standardized studies are required to clearly define its indications and optimal protocols for use [31].

2.3. Autologous adipose tissue transfer

Autologous adipose tissue transfer (AFT) represents a promising regenerative strategy in the treatment of refractory chronic wounds, based on the harvesting and reinjection of the patient's own fat, which is rich in stromal vascular fraction and mesenchymal stem cells (ADSCs). These cells exert beneficial effects through immunomodulation, promoting the transition of macrophages toward an anti-inflammatory profile, reducing chronic inflammation, and stimulating epithelialization and tissue regeneration processes. At the same time, ADSCs secrete paracrine factors that stimulate angiogenesis, fibroblast proliferation, and collagen synthesis, contributing to dermal restoration and improvement of the extracellular matrix [32].

From a clinical perspective, existing studies—primarily case series and observational studies—indicate promising results, with a favorable safety profile and no significant adverse reactions reported to date. There is evidence that the use of adipose tissue, including microfragmented fat, may accelerate healing and reduce hospitalization duration, including diabetic ulcers and associated complications. However, the lack of randomized controlled trials and variability in protocols limit the generalizability of results, and long-term effects remain insufficiently clarified [33,34].

The procedure involves harvesting fat using standardized techniques (such as the Coleman technique), processing it through centrifugation or filtration, and reinjecting it into the wound or surrounding tissues in micro-deposits to promote integration and revascularization. Although complications are rare and the regenerative potential is significant, there are limitations related to costs, standardization, regulation, and the need for long-term risk assessment, including the potential for cellular instability. In conclusion, AFT represents an innovative option, but one that requires further validation through rigorous studies and well-defined protocols to be widely integrated into clinical practice [35].

2.4. Other modern adjuvant therapies

Modern adjuvant therapies in the treatment of chronic wounds primarily include negative pressure wound therapy (NPWT), hyperbaric oxygen therapy, acellular dermal matrices, and modern or advanced dressings. NPWT is particularly useful in cavitary, exudative, or infected wounds, by stimulating granulation tissue formation, reducing edema, controlling exudate, and decreasing bacterial load. Hyperbaric oxygen therapy is mainly used in patients with diabetic ulcers and associated ischemia, by increasing tissue oxygenation, stimulating angiogenesis, and reducing the risk of amputation in selected cases. Acellular dermal matrices function as a scaffold for tissue regeneration; however, their efficacy largely depends on the vascularization of the recipient bed [36,37].

Modern dressings play a role in protecting the wound, maintaining an optimal moist environment, and, in some cases, controlling bacterial or proteolytic load. Alginates, foams, hydrocolloids, and hydrogels are used depending on wound characteristics, while smart hydrogels represent an innovative direction, as they can detect infection, enable controlled release of active substances, and even allow remote wound monitoring. However, many of

these technologies remain limited by issues related to clinical validation and practical implementation [38,39].

2.5. Limitations of regenerative therapies and challenges in implementation

Despite their potential, regenerative and adjuvant therapies face multiple challenges: lack of standardization, variable outcomes depending on wound type and patient status, limited access to equipment and trained personnel, as well as the absence of reimbursement and inclusion in official guidelines. In addition, existing evidence often derives from small and heterogeneous studies. Therefore, for their widespread integration into clinical practice, multicenter studies with large cohorts, long-term follow-up, and rigorous economic evaluation are required.

Chapter 3. Working hypothesis, research objectives, and general methodology

The general hypothesis of the research is based on the premise that regenerative therapies can accelerate the healing of chronic wounds and improve clinical outcomes by stimulating tissue regeneration, modulating inflammation, and optimizing the local microenvironment. At the same time, it is assumed that the efficacy of these therapies is not uniform across all wound types, with certain subgroups being more responsive depending on etiology, vascular status, bacterial load, comorbidities, and the quality of standard care.

On this basis, the overall objective of the research was to evaluate the role of regenerative therapies in the management of chronic wounds in Romania, both from the perspective of their use in current medical practice and their therapeutic effect, as well as the possibility of standardization through protocols adapted to the local context.

To achieve this aim, the research was structured around several specific objectives: assessing the level of use of regenerative therapies in clinical practice, estimating their therapeutic benefit in association with standard care, identifying the types of wounds that respond more favorably to these interventions, and developing pragmatic protocols adapted to the resources and limitations of the Romanian healthcare system.

The methodology followed a multicomponent design, consisting of three complementary pillars.

The first consisted of a structured literature review aimed at synthesizing current evidence regarding the efficacy and limitations of regenerative therapies and identifying knowledge gaps relevant to clinical practice in Romania.

The second pillar was a cross-sectional observational study, based on a questionnaire addressed to physicians involved in the treatment of chronic wounds, with the aim of describing current practices, variability in approaches, the use of regenerative therapies, perceptions of their efficacy, and barriers to implementation.

The third pillar was a prospective clinical study focused on evaluating the evolution of chronic wounds treated with standard care, with or without the integration of regenerative therapies, under real-world clinical conditions. This component included clearly defined inclusion and exclusion criteria, a standardized baseline assessment of the wound and patient,

serial monitoring, and the measurement of relevant clinical outcomes, such as wound surface reduction, time to closure, complications, and the need for additional procedures.

The integration of these three components allowed the correlation of the theoretical framework with real-world clinical practice and direct observations of therapeutic effects, thereby providing a foundation for the development of applicable protocols.

The entire research process was conducted in accordance with ethical principles, including informed consent, confidentiality, data anonymization, and compliance with GDPR regulations.

Statistical analysis was adapted to the type of data and study objectives, including descriptive methods, normality tests, and group comparisons, using a significance threshold of $p < 0.05$ and SPSS software for data processing.

Chapter 4. Study 1 – therapeutic potential of platelet-rich plasma (PRP) in the management of the diabetic foot: literature review and case study (neglected deep plantar abscess)

4.1. Introduction and scientific rationale

This study aims to evaluate the role of PRP in the treatment of diabetic foot ulcers through a comprehensive analysis of the specialized literature, complemented by the presentation of a relevant clinical case—a neglected deep plantar abscess with severe progression and a high risk of amputation.

4.2. Methodology of the literature review

The literature search was conducted in PubMed, including relevant studies on the use of PRP in diabetic foot ulcers (meta-analyses, RCTs, and reviews), published in English between 2010 and 2025. Selection was performed in two stages (title/abstract and full text) by two independent reviewers, in accordance with PRISMA guidelines. Studies analyzing the efficacy of PRP (healing, wound reduction, infection, risk of amputation) were included, while those lacking relevance or methodological detail were excluded.

4.3. Results and synthesis of evidence from literature

A total of 35 eligible studies were included (11 meta-analyses, 15 reviews, and 9 clinical studies) [40,41], all evaluating the use of PRP in diabetic foot ulcers. Most clinical studies demonstrated significant benefits, including accelerated healing, reduction in wound size, and stimulation of granulation tissue, although results varied depending on lesion severity and application technique.

Analyzed studies	Main results	Observations
Yang HA et al. (2025); Smith J. et al. (2024); Peng Y. et al. (2024); Su YN et al.	PRP associated with conventional treatment accelerates wound healing	Improved re-epithelialization and increased wound closure rates

(2023); Qu W et al. (2021); Sridharan K et al. (2018)		
Perussolo J. et al. (2025); Fang X. et al. (2024); Izzo P et al. (2023)	PRP and platelet-rich growth factors (PRGF) reduce wound size and accelerate healing	PRGF demonstrated additional anti-inflammatory benefits
Yin XL et al. (2023); Vicenti G et al. (2018)	PRP is effective and safe in diabetic foot ulcer healing	No severe adverse reactions reported; favorable safety profile
Gomez PT. et al. (2024)	PRP associated with standard treatment leads to superior outcomes compared to standard treatment alone	Randomized clinical trial; significant improvement in healing rates in the PRP group
OuYang H et al. (2024)	PRP reduces amputation rates and adverse events	Decreased need for amputation in high-risk patients
OuYang H et al. (2024)	PRP combined with NPWT is more effective than standard treatment	Synergistic effect on wound healing
Wong AYW et al. (2024); Fang X. et al. (2024)	PRP reduces ulcer-related adverse events (e.g., infections)	Lower infection rates and improved local wound environment
Fang X. et al. (2024); Deng J et al. (2023)	PRP has the potential to reduce amputation risk	Reduced major amputation rates and improved long-term limb preservation

Table 4.1 – Main studies evaluating the efficacy of PRP in the management of chronic wounds, highlighting consistent findings.

Meta-analyses have confirmed the efficacy of PRP as an adjuvant to conventional treatment, including a reduction in amputation rates, particularly when combined with negative pressure wound therapy. In addition, PRP has proven to be safe, with a low rate of adverse reactions and favorable effects on infection control.

4.4. Discussion

Current evidence suggests that PRP has significant therapeutic potential in the management of diabetic foot ulcers, by stimulating tissue regeneration, angiogenesis, and modulating inflammation. However, results are not uniform, with efficacy varying depending on patient characteristics, wound type, and method of preparation and application. PRP can be administered both injectable and topically and may also act on bacterial biofilm, exerting antimicrobial and anti-inflammatory effects that contribute to improving the local wound environment.

Clinical studies and meta-analyses predominantly demonstrate accelerated healing and reduction in wound size, and some suggest a role in decreasing amputation risk, particularly when PRP is combined with other therapies such as NPWT. However, its impact on amputation rates remains inconclusive in some individual studies, although large-scale analyses indicate overall benefits [26]. The lack of standardized protocols and methodological variability explain these discrepancies and highlight the need for further research [42].

In clinical practice, integrating PRP into a multimodal approach, alongside surgical debridement and advanced therapies, may lead to significant clinical outcomes, including limb salvage in severe cases. Thus, PRP emerges as a promising adjuvant therapy, although further validation is required for standardization and widespread implementation [43].

The presented case involved a deep plantar abscess in a diabetic patient, with severe progression and systemic complications, in which amputation was considered likely. Through a multimodal approach—surgical debridement, NPWT, and PRP infiltration—infection control and progressive wound healing were achieved, avoiding limb loss. This example highlights the valuable role of PRP as an adjuvant therapy in the management of complex diabetic foot wounds [44].

PRP may modulate chronic inflammation in diabetic wounds through anti-inflammatory cytokines, contributing to a healing-conducive environment and potentially

reducing neuropathic pain and pathological scarring. However, clinical evidence remains limited, particularly regarding comparisons between different PRP types (e.g., L-PRP vs. P-PRP), with most data derived from preclinical studies [45].

The efficacy of PRP is variable and influenced by factors such as oxidative stress, hyperglycemia, and the inflammatory environment, which may even induce cytotoxic effects and reduce cellular viability. In diabetes, mechanisms such as lipotoxicity and metabolic dysfunction may compromise the therapeutic effect of PRP [46]. Despite these limitations, PRP remains a promising option, and optimization of preparation techniques and the use of biomaterials may improve outcomes. Larger, well-standardized clinical studies are needed to validate its efficacy and safety.

Chapter 5. Study 2 – management of chronic wounds in Romania: assessment of clinical practices and PRP efficacy through a questionnaire-based study

5.1. Introduction

Chronic wounds are characterized by the arrest of the healing process in the inflammatory phase, and the absence of a significant reduction in wound size after several weeks of treatment indicates the need to change the therapeutic strategy. Their management is complex and variable, including standard care (debridement, dressings, infection control), as well as surgical interventions in advanced cases. In this context, regenerative therapies, such as PRP, have gained interest due to their potential to stimulate tissue regeneration; however, their use remains limited by logistical and access-related factors [47–49].

The impact of chronic wounds is often underestimated, although they are associated with major comorbidities and generate a significant burden on the healthcare system. In Romania, although international guidelines exist, their implementation is inconsistent, due to insufficient integration into clinical practice and lack of systemic support [41].

In this context, the study aims to analyze current treatment practices, differences in approaches between specialties, and physicians' perceptions regarding regenerative therapies, particularly PRP, as well as the need to develop standardized national protocols to optimize chronic wound care.

5.2. Materials and methods

The study was designed as a cross-sectional observational study, aiming to evaluate current practices in the management of chronic wounds in Romania and to identify variations according to specialty and initial therapeutic approach. A secondary objective was to analyze physicians' perceptions regarding the use of PRP and the need for standardized protocols.

Data were collected using a structured online questionnaire (37 questions), completed by 240 physicians from relevant specialties (plastic surgery, general surgery, vascular surgery, dermatology), practicing in the public healthcare system. Participation was voluntary and

anonymous, and respondents were selected based on clinical experience and direct involvement in the treatment of chronic wounds.

The analysis included stratification of participants into three groups, according to the initial therapeutic strategy (conservative, surgical, or individualized), and data were statistically evaluated using tests appropriate to the type of variables, with a significance threshold of $p < 0.05$.

5.3. Results

The analysis revealed significant variability in clinical practices regarding chronic wound management, with pressure ulcers, diabetic ulcers, and venous ulcers being the most common. Most physicians initially prefer a conservative approach, and the absence of a standardized protocol is frequently reported.

Wound assessment is primarily based on clinical examination and medical history, while advanced investigations (e.g., ABI, imaging) are more commonly used by physicians who opt for early surgical intervention. In infection management, antibiotic therapy is generally guided by antibiogram results; however, the use of bacterial cultures varies, being more frequent in the surgical group, where infections with resistant pathogens are more commonly encountered.

The use of PRP remains limited (approximately one quarter of respondents), but interest is increasing, with its efficacy perceived as moderate, and access to equipment representing the main barrier. A relevant finding is the majority of physicians' willingness to implement standardized national protocols, considered essential for improving the quality and consistency of care.

5.3. Discussion

The study highlights that the management of chronic wounds is marked by significant variability, influenced by the physician's specialty and experience [50]. In general, most clinicians initially prefer a conservative approach, reserving surgical intervention for refractory cases; however, surgically oriented physicians tend to perform more rigorous diagnostic evaluations (imaging, ABI, cultures), which supports more precise therapeutic

planning. In contrast, the conservative approach relies more heavily on clinical assessment, with the risk of underutilizing essential investigations, particularly vascular evaluation.

Infection control is managed differently: the conservative approach avoids overtreatment of colonization, while the surgical approach prioritizes identification and reduction of bioburden, reflecting the need for a balance between these strategies. Therapeutic decisions, including the use of grafts, are tailored to wound characteristics and clinical objectives, confirming the importance of appropriate patient selection.

Although PRP has a solid biological rationale and a moderate level of confidence among physicians, its use remains limited, mainly due to logistical barriers and lack of standardization. At the same time, modern therapies such as PRGF appear promising but are insufficiently implemented [49,51].

A key finding is the clear need for standardization: physicians support the introduction of national protocols and uniform evaluation systems, which could reduce variability and improve outcomes. However, these protocols must retain sufficient flexibility to allow adaptation to the specific characteristics of each case.

Ultimately, the study emphasizes that optimizing chronic wound management depends not only on therapeutic advancements but also on the integration of guidelines into practice, access to resources, medical education, and patient involvement, including through modern tools such as telemedicine and home-based care.

Chapter 6. Study 3 – application of platelet-rich plasma and autologous adipose tissue transfer in the management of chronic wounds: prospective study

6.1. Introduction

Chronic wounds are lesions that fail to adequately progress through the physiological stages of healing and are clinically defined by the absence of a significant reduction in size within the first weeks or the lack of complete epithelialization within approximately three months. With a prevalence of about 2.5% in Europe and the United States, they represent a major public health issue, with a substantial impact on quality of life and healthcare system costs. Although they predominantly affect the elderly population, incidence is increasing among younger patients as well, in association with comorbidities such as diabetes mellitus, obesity, and peripheral vascular disease. Chronicity results from a complex interaction between local factors (ischemia, infection, necrosis) and systemic factors (metabolic status, immunosuppression, nutrition) and is often sustained by bacterial colonization and biofilm formation, which perpetuate inflammation and impair tissue regeneration [52–54].

The management of these wounds requires a multidisciplinary and individualized approach, in which emerging regenerative therapies are gaining an increasingly important role. Platelet-rich plasma (PRP) provides a concentrated source of growth factors involved in angiogenesis, cellular proliferation, and tissue remodeling, facilitating the transition from inflammation to healing. In parallel, autologous adipose tissue transfer acts through complex mechanisms, including stimulation of angiogenesis, modulation of the immune response, and support of the extracellular matrix. The present study evaluates the efficacy of these therapies, used individually or in combination, within a protocol that includes serial debridement and standardized care, using wound surface area reduction as the primary indicator of therapeutic response [55].

6.2. Materials and methods

The study had a prospective observational design and was conducted between September 2024 and March 2025 in a specialized wound care unit. A total of 35 patients with chronic wounds persisting for more than six weeks were included, all receiving serial surgical debridement and standardized local care, followed by treatment with PRP and/or autologous adipose tissue transfer. Depending on the need for surgical coverage, patients were divided into two groups: one assisted by split-thickness skin grafting (STSG) associated with regenerative therapies, and one treated exclusively with regenerative methods. Inclusion and exclusion criteria were designed to ensure a relatively homogeneous cohort, without active systemic infections or contraindications to autologous procedures.

Clinical evaluation included the collection of demographic data and relevant parameters (comorbidities, etiology, wound size and duration), as well as monitoring of evolution through serial measurements and photographic documentation. The primary endpoint was the percentage reduction in wound surface area, while secondary endpoints included complete healing, infection rate, and the need for adjuvant therapies. In cases with suspected infection, microbiological cultures were performed in accordance with EUCAST standards. PRP was obtained through standardized centrifugation and administered perilesional, while fat grafting was performed using a minimally traumatic technique, with mechanical processing to obtain injectable microfat. The choice of therapy was individualized, and in selected cases the two methods were combined within the same session.

For patients requiring surgical coverage, split-thickness skin grafts were harvested using an electric dermatome, applied onto a properly prepared wound bed, and managed according to standard protocols. All patients received regular dressings and close clinical monitoring. Statistical analysis was performed using IBM SPSS Statistics v.25, with assessment of data distribution באמצעות the Shapiro–Wilk test and the use of appropriate statistical tests (Mann–Whitney, Fisher's exact test, Student's t-test) depending on variable type. The threshold for statistical significance was set at $p < 0.05$.

6.3. Results

The cohort included 35 patients (54.3% male), with a mean age of approximately 59 years, without significant differences between groups. However, relevant differences were

observed: patients who required skin grafting had a significantly higher body mass index, while smoking was more frequent in the group treated exclusively with regenerative methods. From a clinical perspective, most wounds were of venous or diabetic etiology, predominantly located in the lower limb. Wounds in the grafted group were significantly larger and older, suggesting greater severity among cases selected for surgical coverage.

Regarding treatment, most patients underwent a single PRP session, while a smaller proportion also received autologous adipose tissue transfer. Negative pressure wound therapy was more frequently used in the grafted group, with no significant differences in total treatment duration between groups. Comorbidities were comparable overall, although chronic venous insufficiency was more prevalent among grafted patients. From a microbiological standpoint, *Pseudomonas aeruginosa* was the most frequently isolated pathogen and was significantly more prevalent in the grafted group, likely reflecting the increased complexity and chronicity of these wounds.

Clinical evolution showed a median healing progression of 90%, with no significant differences between groups, and a similar complete healing rate (approximately 45%). However, a notable proportion of patients did not show improvement. Inflammatory markers did not differ between groups, but antibiotic use was significantly more frequent in patients who underwent skin grafting, although the duration of antibiotic therapy remained similar. Overall, the results suggest comparable efficacy of the therapeutic strategies, despite the greater initial severity of cases in the grafted group.

6.4. Discussion

The results of this study support the beneficial role of autologous regenerative therapies in the management of chronic wounds, particularly platelet-rich plasma (PRP), as a flexible, safe, and easily integrated method in clinical practice [56]. The cohort consisted predominantly of patients around 59 years of age, mainly male, a profile frequently reported in the chronic wound literature. The analysis showed that patients in the grafted group had a significantly higher body mass index, suggesting a link between obesity and increased wound severity, while smoking was more prevalent in the non-grafted group, possibly reflecting reduced surgical eligibility and confirming the negative impact of smoking on healing. These

findings emphasize that treatment success depends not only on local intervention but also on the control of systemic factors such as metabolic status, body weight, and smoking.

Most wounds were located in the lower limbs, with venous and diabetic etiologies predominating, consistent with international data. Wounds in the grafted group were significantly larger and older, indicating greater complexity and justifying the need for additional reconstructive interventions. Negative pressure wound therapy was more frequently used in these complex cases, while PRP was predominantly administered in a single session, yielding encouraging clinical results. Autologous adipose tissue transfer was mainly reserved for extensive and refractory wounds, where it was used as an adjuvant with potential to stimulate angiogenesis, extracellular matrix remodeling, and local regeneration. The fact that total treatment duration did not differ significantly between groups suggests that the use of these advanced therapies does not unnecessarily prolong the therapeutic process, even in more severe cases.

In terms of efficacy, the median healing progression was 90%, and nearly half of the patients achieved complete healing, with no significant differences between the grafted and non-grafted groups. This suggests that regenerative therapies may contribute to achieving comparable outcomes even in more severe wounds, supporting the idea that they can mitigate prognostic differences between moderate and complex lesions. Colonization with *Pseudomonas aeruginosa* was more frequent in the grafted group, likely reflecting the greater chronicity and severity of these wounds, and the more frequent use of antibiotic therapy in this group followed a clinically justified pattern, without excessive prolongation of treatment duration. At the same time, the absence of significant differences in systemic inflammatory markers supports the safety profile of PRP and autologous adipose tissue transfer, suggesting that these interventions modulate local inflammation without inducing relevant systemic imbalances.

Overall, the results support the inclusion of PRP and autologous adipose tissue transfer in treatment protocols for chronic wounds, particularly in refractory or complex cases. The observed benefits are consistent with the known biological mechanisms of these therapies, including stimulation of angiogenesis, fibroblast proliferation, recruitment of reparative cells, modulation of inflammation, and support of tissue regeneration. However, conclusions should be interpreted with caution, given the relatively small sample size, observational design, lack

of a control group, and clinical heterogeneity of cases. In addition, variability in PRP preparation protocols and adipose tissue processing may affect reproducibility of results. Future research should include randomized controlled trials with larger cohorts, clearly defined therapeutic arms, and standardized protocols, complemented by biological analyses, microvascularization assessments, and cost-effectiveness studies, in order to support the integration of these therapies into standardized clinical guidelines and protocols [57].

Conclusions and personal contributions

The thesis evaluated the role of autologous regenerative therapies, particularly PRP and autologous adipose tissue transfer, in the treatment of chronic wounds in Romania and demonstrated that they can significantly improve healing when integrated into a complex and individualized therapeutic approach.

The objectives were achieved through a multidimensional approach, which included a literature review on PRP in diabetic foot ulcers, a questionnaire-based study on clinical practices in Romania, and a prospective clinical study assessing the efficacy of PRP and fat grafting. The results showed that PRP has the potential to accelerate healing, promote granulation tissue formation, and reduce the time to wound closure, while the clinical study confirmed a complete healing rate of 45.7% and a significant reduction in wound surface area. The combination of PRP with autologous adipose tissue transfer proved superior to conventional approaches in terms of accelerating epithelialization, reducing local inflammation, decreasing the need for antibiotic therapy, and improving wound bed quality. In addition, the questionnaire-based study revealed a high level of interest among physicians in regenerative therapies, as well as substantial variability in clinical practices, explained by the lack of a standardized national protocol, unequal access to resources, and insufficient infrastructure.

The main advantages of these therapies derive from their autologous nature, which confers a favorable safety and tolerability profile, as well as from their ability to directly target the biological mechanisms involved in wound chronicity. However, their implementation is limited by the lack of standardized preparation and application protocols, high costs, limited access to equipment, and the absence of reimbursement within the public healthcare system. Furthermore, the heterogeneity of existing studies, the lack of multicenter randomized research, and limited long-term efficacy data hinder the formulation of strong recommendations.

In conclusion, the thesis supports the need for standardization of PRP protocols, the development of large-scale multicenter studies, the integration of biomarkers in treatment response assessment, and the performance of cost-effectiveness analyses. These steps are essential for the inclusion of regenerative therapies in national guidelines and for the

development of an integrated, interdisciplinary, and personalized approach to chronic wound management.

Personal contributions

1. Conducted a questionnaire-based study on physicians' practices in Romania regarding chronic wound management (Chapter 5), which highlighted the lack of standardized therapeutic protocols, the growing interest in PRP use, and the main barriers to implementing regenerative therapies in clinical practice.

2. Performed a systematic review on the use of PRP in diabetic foot management (Chapter 4), involving critical analysis and synthesis of data from the specialized literature, correlated with the presentation and interpretation of a complex clinical case relevant to the practical applicability of these therapies.

3. Conducted a prospective clinical study evaluating the efficacy of PRP and autologous adipose tissue grafting (Chapter 6), which demonstrated the effectiveness of regenerative therapies and the superiority of combined PRP and adipose tissue therapy in certain types of chronic wounds, with relevant practical implications for reconstructive surgery.

4. Identified real-world limitations in the implementation of regenerative therapies in Romania (Chapters 5 and 6.5), through the integrated analysis of questionnaire-based data and personal clinical experience. This contribution highlighted key barriers to widespread use, including the lack of standardized protocols, variability in application methods, costs associated with equipment and consumables, and limited access within the public healthcare system, representing a strategic contribution to healthcare policy.

5. Proposed directions for national standardization (Chapter 6.5), representing a contribution focused on the practical applicability of the results, aimed at harmonizing chronic wound management in Romania and providing a foundation for the development of clinical guidelines.

6. Published research findings in internationally indexed journals (3 ISI articles), representing external validation of the scientific value of the conducted studies through acceptance in recognized journals indexed in relevant databases. At the same time, publication

in indexed journals contributes to increasing research visibility and supports the validity, reproducibility, and comparability of the presented results.

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