**“CAROL DAVILA” UNIVERSITY OF MEDICINE AND PHARMACY, BUCHAREST**
**DOCTORAL SCHOOL**
**GENERAL MEDICINE**

# ASSESSMENT OF COVERAGE METHODS FOR LOWER LIMB SOFT-TISSUE DEFECTS

## ABSTRACT OF THE PHD THESIS

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## 1. Fundamental problem

The fundamental problem addressed in the present research lies in the extreme complexity and often unpredictable nature of soft-tissue defect reconstruction in the lower limb, a field in which biomechanical demands intersect with severe biological limitations. The central challenge is not merely technical in nature, but rather concerns the survival and functional integration of tissues within a compromised anatomical environment characterized by limited skin extensibility, fragile peripheral vascularization, and frequent exposure of critical vascular, neural, or osteotendinous structures.

The essence of the research problem is defined by the discrepancy between the technical potential of modern microsurgery and the precarious biological conditions of complex wounds. Although advances in free tissue transfer have considerably broadened the spectrum of therapeutic options, the healing process remains vulnerable to critical factors such as limited peripheral perfusion, persistence of bacterial biofilms, chronic inflammation, and metabolic comorbidities, particularly in the setting of diabetic pathology. Thus, the fundamental problem is not confined to the mere coverage of a defect, but rather aims at achieving true predictability in limb salvage, reducing morbidity, and restoring motor function adequate for weight-bearing and ambulation.

In this context, the paper identifies a pressing need in clinical practice: the transition from reconstructive strategies based on subjective assessment to technology-optimized protocols. Uncertainty regarding the optimal timing of intervention and the long-term viability of flaps constitutes a major source of risk for the patient and a significant economic burden on the healthcare system. The research focuses on addressing this limitation through the integration of innovative adjunctive methods.

The problem is approached in a multidimensional manner through the evaluation of the efficacy of negative pressure wound therapy combined with silver nanoparticles, intended to counteract the inflammatory and infectious environment, and through the use of infrared thermography as a non-invasive monitoring tool. Thus, our objective was to eliminate the uncertainty associated with complex reconstructive procedures by employing readily predictable therapeutic protocols and state-of-the-art technologies. The ultimate goal is to ensure viable socio-professional reintegration of patients, significantly reduce the risk of amputation, and redefine standards of care in this highly complex surgical field.

## 2. Working Hypothesis and Research Objectives

The present research establishes the strategic direction of the thesis by recognizing the lower limb as a complex structure that is essential not only for the mechanical functions of support and locomotion, but also for the psychological balance and social integration of the individual. In this context, reconstruction of soft-tissue defects extends beyond the mere surgical act of wound coverage, becoming a process of multidimensional rehabilitation.

The working hypothesis of these doctoral studies is based on the premise that a holistic approach to lower limb reconstruction, in which restoration of functional and biomechanical integrity is synergistic with aesthetic reconstruction, leads to superior clinical outcomes. This research was initiated from the hypothesis that, through this integrative paradigm, it is possible to achieve not only a significant reduction in mortality rates and postoperative immobilization periods, but also effective prevention of social isolation, thereby facilitating the professional and economic reintegration of patients. Thus, therapeutic success is defined by the ability to transform a traumatized or pathologic limb into a segment capable of weight-bearing, able to support the patient's independence and self-image.

In order to validate this hypothesis, the study establishes the following main objectives:

- To highlight the systemic benefits of lower limb reconstruction and the resumption of ambulation.
- To optimize the selection of reconstructive methods by developing rigorous decision-making criteria, correlating the anatomical characteristics of the defect with the pathophysiological profile and the specific comorbidities of each patient.
- To evaluate complication rates and their prevention through the identification of perioperative risk factors and the implementation of targeted prophylactic measures.
- To determine the extent to which modern tools such as thermography or negative pressure wound therapy can anticipate flap failure or optimize graft integration, thereby ensuring a favorable postoperative course.

## 3. Research Methodology

The research adopts a mixed methodology, structured around three complementary pillars, designed to evaluate the efficacy and predictability of lower limb reconstruction methods through the integration of modern technologies already available in current medical practice. The prospective clinical studies were conducted between September 2022 and January 2026 within the Department of Plastic Surgery of the "Prof. Dr. Agrippa Ionescu" Emergency Clinical Hospital and followed two divergent yet complementary directions:

- A comparative study evaluating graft integration using negative pressure wound therapy combined with silver nanoparticles versus conventional postoperative management (tie-over dressing).
- An assessment of the efficacy of infrared thermography in the preoperative identification of perforator vessels and in the postoperative monitoring of flap viability.

Cohort selection was based on rigorous criteria. Adult patients with soft-tissue defects treated with grafts or perforator-based flaps, who provided informed consent, were included. Patients with unacceptable anesthetic risk, sepsis, major psychiatric disorders, or poor therapeutic compliance were excluded. The research complied with ethical and deontological standards, as well as with current regulations regarding personal data protection.

The statistical analysis addressed demographic variables, comorbidities such as diabetes mellitus or vasculopathies, paraclinical parameters, and defect characteristics. Data were processed using IBM SPSS Statistics version 26.0. Nominal association tests ($\chi^2$), mean comparison tests such as ANOVA or Student's t-test, and Pearson correlation coefficients were applied, with the threshold for statistical significance set at $p < 0.05$ (95% CI).

The systematic review and meta-analysis, conducted in accordance with PRISMA guidelines, focused on the performance of the anterolateral thigh free flap in diabetic foot reconstruction. Study identification involved an exhaustive search of international databases (PubMed, Scopus, Web of Science, Embase, and Cochrane). Study selection was performed by two independent reviewers, and the data were integrated using a random-effects model. Heterogeneity was quantified using the $I^2$ statistic and Cochran's Q test, while publication bias was assessed with graphic funnel plots and Egger's test. Through this methodological architecture, the thesis ensures rigorous validation of its hypotheses by combining direct clinical experience with evidence derived from the scientific literature.

## 4. Current State of Knowledge

### 4.1. Anatomical and Biomechanical Considerations

The lower limb has a stratified tissue architecture composed of skin, subcutaneous adipose tissue, superficial fascia, and deep fascia, each fulfilling essential biomechanical and protective roles. The skin is thicker and more resistant than that of the upper limb, reflecting its adaptation to upright posture and mechanical loading. The plantar region is characterized by a dense cutaneous-subcutaneous layer, with fibrous septa and compartmentalized adipose tissue that attenuate pressure during gait [1].

Regional vascularization is organized around the main arterial axes (femoral, popliteal, tibial, and peroneal arteries). Modern reconstruction was revolutionized by the angiosome concept, introduced by Taylor and Palmer in 1987, which defines the body as being composed of three-dimensional blocks of tissue supplied by a source artery. These units are interconnected through direct anastomoses (of constant caliber) and indirect anastomoses (choke vessels) [2]. Subsequently, the perforasome concept, introduced in 2009, refined this perspective by defining the territory supplied by a single perforator vessel. The lower limb contains approximately 90–100 perforating arteries, allowing predictable design of modern flaps without sacrificing the underlying muscle [3].

The biomechanics of bipedal gait is a cyclical process involving the stance phase and the swing phase. Of critical importance is the pulley mechanism described by Hicks, which is activated during extension of the hallux, tensioning the plantar fascia and transforming the foot into a rigid lever essential for effective propulsion. Any pathology that interferes with this mechanism, such as diabetes mellitus or plantar fasciitis, compromises gait stability and dynamics [4,5].

### 4.2. Physiology and Pathophysiology of Wound Healing

Tissue healing is a complex process that unfolds through the sequential phases of hemostasis/inflammation, proliferation, and remodeling. The initial injury induces local hypoxia, which activates a metabolic shift from oxidative phosphorylation to aerobic glycolysis (the Warburg effect). Macrophages predominate within the wound between days 2 and 7 and regulate the transition toward the proliferative phase through cytokines such as TGF-β1 and VEGF. The final scar ultimately recovers only approximately 80% of the skin's original tensile strength [6,7].

Diabetes mellitus represents a major barrier to wound healing by inducing oxidative stress, endothelial dysfunction, and a persistent proinflammatory milieu. The diabetic environment promotes macrophage polarization toward the M1 (proinflammatory) phenotype, thereby inhibiting transition to the M2 (reparative) phenotype. The diabetic ulcer is the principal precursor of most non-traumatic amputations and is associated with a five-year mortality rate exceeding 50%, surpassing that of many oncologic diseases [8].

A critical factor in the chronicity of wounds is the bacterial biofilm, defined as a structured microbial consortium adherent to surfaces. Biofilm impedes the natural progression of wound healing by conferring protection against antibiotics and host immune defenses, thereby creating an environment increasingly controlled by microorganisms to the detriment of the host [9,10].

### 4.3. Reconstructive Strategies

The etiology of soft-tissue defects is multifactorial, ranging from post-traumatic causes to defects resulting from metabolic-vascular pathology or post-oncologic conditions. This aspect is of major importance in clinical reasoning, as it has a significant impact both on the choice of reconstructive method and on patient prognosis.

Reconstructive strategies have evolved from the classical "reconstructive ladder" to more dynamic concepts:

- The reconstructive elevator: This allows the surgeon to directly select the optimal solution, regardless of complexity [11].
- The reconstructive grid: A three-dimensional approach that integrates surgical complexity, technological resources, and individual patient-related factors [12].

The timing of reconstruction is essential for success. The **"fix and flap"** concept, applied to Gustilo-Anderson type IIIB open fractures, involves definitive fracture stabilization and soft-tissue reconstruction within a single procedure during the first 72 hours after trauma, significantly reducing the risk of osteomyelitis [13].

### 4.4.Coverage Techniques

Skin grafts are fundamental in the management of extensive defects; however, their success depends on adequate vascularization of the recipient bed, and they are contraindicated over denuded bone or exposed tendon [14]. Local and regional flaps provide coverage with adjacent tissues of similar characteristics. Muscle flaps are indicated for complex three-dimensional defects, as they obliterate dead space and contribute to infection control. Perforator-based fasciocutaneous flaps offer superior aesthetic advantages while maintaining robust vascularity. Free microvascular flaps represent the treatment of choice for complex defects, particularly in the distal third of the leg and at the level of the foot, where local options are limited. The anterolateral thigh flap has become established due to its versatility, allowing tissue transfer with minimal donor-site morbidity [15].

### 4.5. Adjunctive Therapies and Regenerative Medicine

Negative pressure wound therapy has become a standard modality in wound bed preparation, stimulating angiogenesis and обеспечивая a graft take rate of approximately 97.5% [16]. Hyperbaric oxygen therapy corrects tissue hypoxia, reduces edema, and is essential in the management of necrotizing infections through its toxic effect on anaerobic microorganisms [17].

Hirudotherapy is indicated as a salvage option in venous insufficiency of flaps, its efficacy being derived from hirudin, a thrombin inhibitor present in leech saliva. However, the risk of *Aeromonas* infection necessitates prophylaxis with fluoroquinolones [18].

Regenerative biotechnologies, such as PRP (platelet-rich plasma) and PRF (platelet-rich fibrin), biologically optimize the recipient bed through the controlled release of growth factors, including PDGF, VEGF, and TGF-β [19,20]. Stem cell-based therapies support healing through paracrine signaling and reduction of inflammation [21].

### 4.6. Amputation

Amputation remains a major intervention with a profound impact on quality of life and mortality, with a median survival of 2.99 years following major amputation. Diabetes mellitus is responsible for 50–70% of cases worldwide. Nevertheless, amputation may represent a functionally superior solution compared with preserving a non-functional or life-threatening limb. Management of phantom limb pain, which has a prevalence of 60–80%, is essential for successful prosthetic rehabilitation [22].

### 4.7. Future Directions

The evolution of surgery is moving toward precision and regeneration. Acellular dermal matrix improves the quality of repair and graft pliability by inducing angiogenesis without pathological collagen accumulation [23].

Ultra-high-frequency ultrasonography (above 25 MHz) enables visualization of minute vascular structures and has become indispensable in microsurgical planning [24]. A major innovation is represented by **superthin flaps** and **pure skin perforator flaps**, which allow the achievement of thin, pliable coverage comparable to a graft, yet with the robust axial vascularization required for survival in challenging environments such as the diabetic foot [25].

# 5. Personal Contributions

## 5.1. Integration of Negative Pressure Wound Therapy with Silver Nanoparticle Dressings in Skin Grafting Procedures

Skin grafting is a fundamental technique in plastic and reconstructive surgery, representing an indispensable solution for the closure of a wide range of cutaneous defects. However, successful graft take is directly conditioned by the dynamics of the postoperative environment and is frequently threatened by fluid accumulation, infection, or mechanical instability, all of which hinder the establishment of essential vascular connections. In order to optimize these outcomes, the present research investigates the synergistic use of negative pressure wound therapy in combination with silver nanoparticle-based dressings [26].

From a pathophysiological perspective, NPWT acts through the continuous evacuation of exudate and the application of macro- and microdeformational forces that promote wound edge contraction. At the molecular level, this therapy modulates the immune response by reducing the concentration of proinflammatory cytokines such as TNF-α and IL-6, while stimulating the secretion of angiogenic and anti-inflammatory factors, including VEGF and IL-10. Complementarily, silver nanoparticles exert an antimicrobial effect through disruption of bacterial enzymatic systems. In addition, they play an active immunomodulatory role by promoting macrophage polarization toward the regenerative M2 phenotype, thereby accelerating re-epithelialization and reducing oxidative stress that could otherwise delay the reparative process [27,28].

The prospective clinical study conducted on a cohort of 80 patients demonstrated a clear statistical superiority of the combined protocol compared with conventional tie-over methods. The results showed a mean graft integration rate of 99.62% at 14 days postoperatively in the NPWT+AgNP group, compared with 93.41% in the control group. A particularly relevant finding is that the benefit of this approach was far more pronounced in patients with severe comorbidities, such as diabetes mellitus or cardiovascular disease, in whom the biological barriers to healing are substantial.

Moreover, the efficacy of the method increased in direct proportion to defect size, with the effect size being considerably greater for extensive grafts exceeding 500 $cm^2$, where the intrinsic risk of failure is high. This favorable evolution was further supported by serial monitoring of C-reactive protein, which showed a significant decrease on postoperative day 10 in patients treated with the combined therapy, confirming the protocol's capacity to effectively modulate systemic inflammation. Thus, we developed an optimized therapeutic protocol that transforms the management of complex chronic ulcerations and large soft-tissue defects into a predictable and sustainable surgical procedure.

### 5.2. Investigation of Perforator-Based Flaps Using Infrared Thermography

Reconstruction of lower-limb soft-tissue defects remains one of the greatest challenges in plastic surgery, with the fundamental objectives of limb salvage and restoration of function in regions characterized by limited tissue mobility and frequent exposure of critical structures. In this context, although regenerative technologies have advanced considerably, locoregional perforator-based flaps continue to represent an essential reconstructive option, providing tissues with characteristics similar to those of the recipient site and a robust axial vascular supply. However, the predictability of these procedures depends critically on the accuracy of vascular pedicle identification and on postoperative monitoring of flap viability—issues that the present research addresses through the use of infrared thermography and Doppler ultrasonography [29].

The study, conducted on a cohort of 76 patients, demonstrates that the integration of these non-invasive methods significantly enhances clinical safety, achieving a flap survival rate of 100%. During the planning phase, infrared thermography showed a sensitivity of 97.4% in the detection of perforator vessels, proving to be a superior tool for initial mapping, while Doppler ultrasonography provided the necessary validation by confirming vascular patency. A major finding indicates that reconstructive success is directly proportional to the vascular density confirmed intraoperatively: flaps with optimal healing incorporated a mean of 2.15 perforators, compared with only 1.33 in those that developed complications.

The research also highlighted the importance of geometric considerations in flap design. In V-Y advancement and Keystone flap techniques, undersizing relative to the defect generated excessive tension at the suture line, thereby compromising marginal microcirculation. By contrast, in propeller flaps, oversizing of the cutaneous island relative to the pivot point increased the risk of distal necrosis due to insufficient perfusion pressure.

Systemic factors exerted a decisive influence on clinical outcomes. Diabetes mellitus was the strongest predictor of complications ($p < 0.001$), with all unfavorable outcomes occurring in patients with this diagnosis. Furthermore, preoperative hyperglycemia (>181 mg/dL) and elevated C-reactive protein levels were identified as major risk markers for tissue compromise.

Postoperatively, monitoring by infrared thermography enabled identification of a thermal signature of complications, characterized by persistent local hypothermia. A thermal gradient greater than 1.19°C compared with the surrounding tissue at seven days after surgery constituted a warning indicator, with predictive power superior to that of subjective clinical assessment. Thus, thermography emerges as a rapid and objective modality for validating reconstructive success and guiding early intervention in cases of vascular compromise.

### 5.3. The Anterolateral Thigh Flap in the Reconstruction of Defects Associated with the Diabetic Foot: Systematic Review and Meta-Analysis

The present review analyzes the scientific evidence regarding the use of the anterolateral thigh free flap in the reconstruction of complex diabetic foot defects, a condition with a massive global impact affecting approximately 529 million individuals. Diabetic foot ulcerations are responsible for more than 85% of lower-limb amputations and are associated with a 5-year mortality rate exceeding 70%. The management of these lesions is hindered by the pathological triad of neuropathy, vascular insufficiency, and impaired healing capacity, frequently compounded by persistent inflammation and bacterial biofilms [30].

In this critical clinical context, microvascular free tissue transfer represents a first-line limb salvage strategy. The ALT flap has become established as a fundamental technique because of its versatility, providing a pliable cutaneous paddle, a long vascular pedicle, and minimal donor-site morbidity. Its resistance to shear forces makes it particularly suitable for weight-bearing regions of the foot [31].

The results of the meta-analysis, which included six retrospective cohort studies encompassing 162 patients, confirm the remarkable efficacy of this approach. The overall pooled flap success rate was 81.8%. Statistical analysis demonstrated a low rate of total flap failure, of only 5.2%, whereas partial necrosis was reported in 13.0% of cases, reflecting the specific vascular challenges of the diabetic population. Technical success was accompanied by excellent functional outcomes: 95.2% of patients were able to return to ambulation.

It is noteworthy that these results were achieved in the setting of an extremely high-risk profile. The studied patients exhibited poor glycemic control (mean HbA1c of 9.9%), a high prevalence of osteomyelitis (63.7%), and peripheral arterial disease (54.3%). Despite these comorbidities, the incidence of postoperative complications was low, with an infection rate of 5.1% and an ulcer recurrence rate of only 1.7%.

In conclusion, reconstruction with the ALT free flap not only ensures anatomical preservation of the lower limb, but also restores quality of life through functional recovery documented by clinical scores such as ASAMI and AOFAS. This review further supports the status of this flap as a robust and reliable reconstructive tool, capable of providing durable tissue stability in the complex management of the diabetic foot.

## 6. Conclusions

This doctoral thesis rigorously integrates the theoretical foundations of the healing process with original clinical data, demonstrating that successful lower limb reconstruction depends on a holistic and technology-driven approach. The research objectives were achieved through the validation of reproducible protocols that transform the management of complex wounds into a predictable procedure, leading to the following conclusions:

- The combined use of negative pressure wound therapy and silver nanoparticles demonstrated clear statistical superiority, achieving a graft take rate of 99.62% at 14 days, compared with 93.41% for conventional methods ($p < 0.001$).
- Infrared thermography is confirmed as a highly accurate non-invasive tool for perforator vessel detection, with a sensitivity of 97.4%, comparable to that of Doppler ultrasonography.
- Tissue compromise can be objectively anticipated through the persistence of a thermal gradient >1.19°C at 7 days postoperatively.
- The patient's metabolic profile is decisive, as a mean blood glucose level of 181.22 mg/dL was directly correlated with the occurrence of complications, underscoring the need for preoperative optimization.
- The meta-analysis confirms the ALT free flap as a robust solution for diabetic foot reconstruction, with an ambulation success rate of 95.2% and a minimal risk of total necrosis (5.2%).

The original contribution of the present work lies in the rigorous transformation of theoretical principles into quantifiable clinical algorithms, successfully applied within a real multidisciplinary setting. This undertaking was methodologically supported through the design and implementation of three complementary research directions, consisting of two prospective studies and one systematic review conducted in accordance with PRISMA standards. These enabled the establishment of standardized assessment time points, which are essential for increasing the predictability of surgical outcomes.

A central component of the personal contribution is the development of optimized treatment protocols for the postoperative management of grafts and flap monitoring, thereby providing reproducible models for routine clinical practice. Innovation in the field of monitoring was marked by the introduction and validation of thermal parameters, such as absolute and relative temperatures, which proved to be valuable functional tools for guiding therapeutic decision-making.

At the same time, the thesis establishes a solid foundation in international scientific evidence through the quantitative synthesis of the literature on the anterolateral thigh flap, providing a necessary interface between local clinical experience and global standards of care in the complex pathology of the diabetic foot. Overall, the thesis proposes a stratified decision-making model, structured around the logical sequence of defect analysis, the patient's biological profile, and objective monitoring, thereby opening concrete perspectives for treatment standardization and the sustainable improvement of patients' quality of life.

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## LIST OF SCIENTIFIC PUBLICATIONS

1. **Abu-Baker, A.**, Ţigăran, A. E., Peligrad, T., Ion, D. E., Gheoca-Mutu, D. E., Avino, A., Hariga, C. S., Moraru, O. E., Răducu, L., & Jecan, R. C. (2024). Exploring an Innovative Approach: Integrating Negative-Pressure Wound Therapy with Silver Nanoparticle Dressings in Skin Graft Procedures. *Journal of personalized medicine*, *14*(2), 206. https://doi.org/10.3390/jpm14020206
   Original article, ISI, impact factor – 3.0.
   Chapter 5, page 44
2. Răducu, L., Moraru, O. E., Gheoca-Mutu, D. E., Peligrad, T., Ţigăran, A. E., **Abu-Baker, A.**, Ion, D. E., Ursuţ, B. M., Jecan, C. R., & Avino, A. (2024). Confronting a New Challenge in Plastic Surgery: MDR Infections in Patients with Chronic Wounds. *Life (Basel, Switzerland)*, *14*(4), 444. https://doi.org/10.3390/life14040444
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3. **Abu-Baker, A.**, Ţigăran, A. E., Timofan, T., Ion, D. E., Gheoca-Mutu, D. E., Avino, A., Marina, C. N., Tulin, A. D., Raducu, L., & Jecan, R. C. (2025). Mapping Perfusion and Predicting Success: Infrared Thermography-Guided Perforator Flaps for Lower Limb Defects. *Medicina (Kaunas, Lithuania)*, *61*(8), 1410. https://doi.org/10.3390/medicina61081410
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