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Chapter 11

Ischemic Ulcer Healing: Does Appropriate Flow Reconstruction Stand for All That We Need?

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Additional information is available at the end of the chapter

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Abstract

During the recent decades, soaring progresses in vascular disease knowledge, particularly in critical limb ischemia (CLI) treatment, enhanced novel diagnostic and interventional strategies with high serviceableness in patient's selection, arterial recanalization, and dedicated ischemic ulcer follow-up. However, despite undeniable advances in medical technology and clinical judgment, limb salvage, the ambulation recovery, and patient's survival seem only scarcely affected in this heterogeneous CLI group, particularly concerning the diabetic and renal patients. Innovative strategies such as "*end artery occlusive disease*" treatment or "*wound-targeted revascularization*" were equally proposed by following the angiosomal anatomical distribution associating individual foot collateral assessment in a unified *macro-* and *micro*-circulatory judgment. However, despite encouraging clinical results, prospective evidence still lacks on this concern. It also appears that specific wounds could not always stand for the lowest perfusion areas according to current CLI criteria, since severe neuropathy, inflammatory swelling, local infection, and skin trauma may add complementary hindrances to tissue viability.

The present chapter endeavor to summarize main available treatment principles for ischemic ulcer recovery that every modern practitioner eventually disposes in an updated contemporary view."

Keywords: wound healing, critical limb ischemia, diabetic foot, angiosome, limb re-vascularization

Motto: '*Each ulcer is unique in complexity and deserves flexible understanding and control of whole individual tissue recovery challenges*' (Current clinical observation)

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1. Introduction

During centuries, wound healing was believed to be part of a mysterious process that addresses only inspirational approaches of secret practitioner's experience. Outstanding scientific advances over the last 50 years revealed real complexity of this staged process, astonishing as life's unfolding itself. This natural course seems to bear thousands of overlapping and indissoluble processes [1]. Today's knowledge, beyond new high-performance techniques for revascularization and tissue engineering [1], affords additional key data about intimate mechanisms of ischemic threat, ulcer formation, and steps to wound recovery [1, 2]. In the recent decades, this proper knowledge enhanced complementary diagnostic and interventional strategies with high serviceableness in patient's selection, arterial recanalization, and dedicated ulcer follow-up [1, 3]. However, despite soaring progress in medical technology and clinical judgment for critical limb ischemia (CLI) wound treatment, limb salvage, and patient's survival seem only scarcely affected [1–3]. This assertion dwells particularly true in diabetic and renal patients who exhibit ischemic foot wounds [1, 2]. Outstanding advances in basic research and clinical management toward better tissue regeneration, unfortunately, seem to confront with parallel increasing of CLI subjects each year [1]. It becomes obvious nowadays that ischemic ulcer healing implies a convergent treatment for multifaceted presentations in patients with multiple arterial and systemic affectations [1–3].

The present chapter endeavor to summarize main treatment principles for CLI ulcer recovery that every modern practitioner eventually disposes in an updated contemporary view.

2. Historical perspectives and advancements in ischemic wounds treatment

Wound healing approaches are probably old as the history of medicine. During centuries, several significant breakthroughs, however, marked significant progress in wound repair, following thorough scientific understanding. Starting with the Ancient World, according to the oldest medical record found on a Sumerian clay tablet (2100 BC) [4], cleansing and bandaging the wound was noted to represent the central "healing gestures" to be practiced in the healing course [4]. The Ancient Egyptians (1600 BC–1550 BC) also mention the use of mixtures (honey, grease, and lint) for wound regeneration, however, without apparent etiologic segregation [5, 6]. They also displayed an impressive science of bandaging, including herbal extracts and resins (probably the first coordinated bandages ever mentioned) [5]. Hippocrates in the ancient Greece originally devised approach methods for acute and chronic wounds [6]. Later on, Cornelius A. Celsius marked a momentous step in wound care history by his original description of the "four cardinal signs of inflammation," including first "gangrenous foot" delineation in his eight-volume *Compendium of Medicine* (41 BC) [6]. A substantial contribution to ulcer's classification and healing understanding is appointed by outstanding surgical work of Ambroise Parré in the Renaissance era about the treatment of gunshot wounds including "the gangrenous battlefield limb" [7]. During the next centuries, many new ideas in wound management were unfortunately rejected by lack of validation and

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time-related historical tendencies. Wound healing understanding was subsequently developed by Joseph Lister's [8] and by Louis Pasteur's remarkable clinical research [8, 9] adding relevant knowledge for bacterial colonization and sepsis development, particularly in the ischemic ground [9]. More recently, notable breakthroughs in comprehending the complexity of wound healing cascade were added by Virchow [10], owning establishment of histopathology as an autonomous discipline [6, 10], and by first isolation of "epidermal growth factor" as a mitotic stimulant in 1962 [11].

Probably one of the most ponderous discoveries in the same period was the defining structure of DNA and RNA by Franklin, Watson, and Crick [6]. Parallel advances were noted in surgical and interventional revascularization techniques for *tissue healing* perceived in a hemodynamic ischemic perspective. Leading milestones in arterial flow imaging were marked by first arteriographic diagnostic reported by Brooks in 1924 [12], followed by first translumbar aortography described by Dos Santos in 1929 [13], both with considerable influence in more accurate inferior limb arterial disease diagnostic. First Doppler ultrasound assessment of atherosclerotic occlusive disease by noninvasive method was reported by Strandness [14] in 1966. All these diagnostic methods have borne huge influence first in distinguishing arterial from nonischemic wounds, and further for separating arterial from venous limb ulceration. The current ischemic injury diagnostic era yet institutes since the computed tomography (CT) scanning and magnetic resonance imaging (MRI) have become an integrated part of ongoing peripheral arterial flow evaluation [15]. For that arterial surgery enables high limb salvage nowadays, the achievement of several important steps was mandatory. The first lumbar sympathectomy in 1924 by Labat [16], the heparin use since 1937 [17], the Kunlin's first saphenous vein graft in 1951 [18] and the first Dacron [19], and polytetrafluoroethylene (PTFE) [20] prothesis utilization, all had tremendous influences in modern surgical revascularization for wound healing [1–3, 20].

Traditionally during years, open surgical bypass represented the main effective treatment strategy for tissue recovery and limb salvage [1, 21]. In addition to outstanding surgical revascularization advances, new transcatheter endovascular techniques emerged and rapidly evolved in CLI treatment arena during the last three decades [21]. They seem to improve the perioperative morbidity-mortality and the length of hospital stay, affording comparable limb preservation rates [1–3, 21]. Owning remarkable low invasiveness and reproducibility, the percutaneous transluminal angioplasty (PTA) and stenting (first promoted by Gruntzig in 1974 and by Dotter [20] in 1964) rapidly gained a wide utilization in the coronary, but also in the peripheral arterial disease (PAD) current treatment [21]. Although the "stent" term derives from Charles Stent (1807–1885), an English dentist who used this term for creating customed dental molds [21], the idea to modulate vascular lumen by diligent metallic implants had great issues in vascular practice. During the next decades, new "bare" or "covered stents" were imagined, together with new "stent grafts" originally pioneered by Volodos and Parodi in the treatment of aortic aneurysmal disease around 1985–1990s [22]. Novel "drug eluted" devices including balloons and stents have been successfully launched during the last decade with promising clinical results [1, 21].

Following parallel scientific emancipation, new strategies as to improve ischemic tissue healing were cast in parallel medical disciplines. Thus, in 1987, Taylor and Palmer initially described the "angiosome" model of human body vascularization [23] and auspiciously implemented the concept among particular plastic reconstructive surgery applications. This significant breakthrough in tissue perfusion understanding was succeeded by its first use in CLI limb salvage by Attinger and colleagues 20 years later [24], using "topographical" or angiosome-guided bypasses to the foot ischemic wounds [24]. Not surprisingly, starting with 2008–2010s, and up to the contemporary period, new endovascular "wound-directed" revascularization applications were described with promising wound healing and limb preservation results [25, 26]. All these progresses have added and undoubtedly will add complementary understanding in ischemic ulcer treatment, owning more precise revascularization selection since specific "wound-targeted" revascularization is performed [24–26].

3. Demographics, etiologic factors, and social implications of PAD with its most severe presentation represented by critical limb ischemia

Recent demographic data suggest that more than 200 million individuals worldwide suffer from varied forms of the PAD that represent a 24% increase over the last decade and concern all socioeconomic strata [27, 28]. The economic weight of PAD was proven to be ponderous [28]. It has meant that the total costs of vascular-related hospitalizations climbed to 21 billion dollars in the USA in 2004, and this threshold seems to rise each year continually [28]. Critical limb ischemia as a consequence of severe infra-inguinal atherosclerosis embodies extreme forms of PAD and currently associates rest pain and ischemic ulcers (corresponding to Fontaine stages III/IV and Rutherford categories 4-5 ischemic limb presentations) [1–3].

The term of CLI is commonly used for patients who exhibit symptoms of severe arterial hypoperfusion for more than 2 weeks [3, 27]. Elementary CLI diagnosis is made by clinical exam, anatomical stratification, and hemodynamic evaluation of flow disturbances over accessible arterial paths [1, 3, 27]. Defining and analyzing large CLI groups of patients, however, prove to be difficult [2–4].

These hindrances are mainly determined by (1) the vast heterogeneity of underlying arterial diseases [1, 27], (b) the various appended risk factors [1–3, 27], (c) the multilevel spread of arterial lesions [1, 27] (d) by concurrent systemic pathologies [27], (e) the scarce follow-up data [3, 27], and (f) the lack of synchronous macro- and microvascular apprehension for gradual hypoxic limb changes [1, 27–31]. It is known that without precocious recognition and aggressive treatment, CLI invariably inflicts significant morbidity and high rates of major amputation and mortality [1–3, 27–30].

To date, the likelihood of death within the first 6 months of CLI diagnosis has been estimated to reach 20% (all etiologies confounded) and exceeds 50% at 5 years following prime documented onset [27–32]. Contemporary studies reveal that patients with PAD (and particularly those with CLI) are more likely to experience simultaneous coronary or cerebral vascular disease, bearing a higher risk of early death [1–3, 27]. The risk for developing PAD seems

considerably increased in diabetic and renal patients, prone to more frequently experience systemic ischemic events compared to general population [1–3, 27–31].

Several risk factors that lead to lower limb major amputation in patients having ischemic wounds were described, including increasing age, being male, being African American, having peripheral neuropathy, and developing infected ulcers [1, 2, 27–29]. The Trans-Atlantic Inter-Society initial Consensus (TASC) II document showed that more than 15% of diabetic subjects will unfold a foot ulcer during their lifetime while 14–24% of them, unfortunately, will require amputation [3]. It is also valued that more than 170 million people suffer nowadays from diabetes mellitus, and their worldwide number is anticipated to attain 366 million by 2030 [1]. In this particular cohort of diabetic patients during the first year of CLI diagnosis, 40–50% among them may experience foot amputation while 20–25% among them will die [1, 2, 27].

Nevertheless, by applying optimal revascularization and local wound treatment as early as possible, up to 85% of amputations can be prevented [3].

The social burden of the metabolic syndrome and particularly the diabetic systemic atherosclerotic disease is tremendous for the patient, the medical care organization, and public communities [1, 2, 28, 31].

Particularly concerning *arterial* inferior limb *ulcers* (all arterial pathologies confounded), current reports document 18–29% prevalence among 60 years or older patients who interestingly bear equal rates as much younger (50-year-old) individuals associating diabetes or tobacco use [33].

4. Critical limb ischemia ulcers: do we meet the current clinical needs?

Postischemic tissue recovery implies simultaneous alignment of several distinct physiological processes [33]. Inasmuch their entire clinical signification remains only partially controlled [27, 30, 33], their unaltered unfolding dwells prerequisite. Among numerous molecular and cellular events that clearly overpass the purposes of this chapter, some practical aspects may be however useful to be highlighted and are briefly summarized in the sections below.

4.1. Leading physiological mechanisms in wound recovery and appended phases of revascularization

It is accepted that mechanisms concerning tissue regeneration are strongly influenced by the type and thickness of tissue layer affectation, also by their capacity for healing [1, 33]. The retrieval of CLI threat resets in motion the regular "cascade" of reconstructive tissue events leading in normal circumstances (absence of systemic risk factors for healing) to long-lasting tissue repair [33, 34]. Full-thickness wound regeneration following most CLI revascularizations concerns the skin, the underlying subcutaneous and the deep muscular compartments. Currently, this process is depicted in three schematic phases: the inflammatory stage (the "lag" phase), the "tissue formation" (or the "proliferative") phase, and the "tissue remodeling" phase [34]. It is important to note that this "allotment" is somewhat conventional since all three

stages are commonly overlapping to some degree [33, 34]. Activating cells that participate in one phase usually produce biological triggers indispensable to interlock tissue molding into the next phase [34]. These stages are routinely *conditioned* by initial hemostasis and by intentional *arterial revascularization*, both representing fundamental activating processes [33–35]. Most details concerning these enthralling multimodal events are largely depicted in available histopathology literature and will not be further characterized in this section.

During the same sequential process, the ischemic burden relief sets in motion three parallel *hemodynamic* regenerative phases [35]. These stages are conceptualized as (1) *the initiatory* flow redistribution phase (concerning "large" remnant collaterals surrounding the ischemic wound zone), (2) *the early* or "mid-term" flow dispensation (regarding the "rescue" or "small" collaterals and arterioles), and (3) *the retarded* postischemic phase, essentially characterized by the arteriogenesis, the angiogenesis processes [33–35]. Alike most biological chain-processes, these three flow-redistribution phases exhibit specific time overlapping in their activation, according to concomitant vascular risk factors and individual patterns of arterial occlusive disease [35]. This particular knowledge may enable the clinician to choose better appropriate diagnostic and treatment methods in a timely approach for every ischemic wound follow-up [33, 35].

4.2. Main pathophysiological aspects in ischemic wound healing and related clinical presentations

To date, the exact mechanisms and time periods conducting to chronic ischemic ulceration are not completely understood [30, 31, 33, 34, 36]. Most arterial ulcers are encountered over the age of 65 as people live longer nowadays [3, 33]. Arterial ulcers are ranked to constitute about 12–19% among all leg ulcers [33, 37] while mixed venous-arterial or combined neuro-ischemic tissue defects may concern 15% [37] up to 24% [29–31] of these patients, respectively. There were described either as "spontaneous" ulcerations (typically involving the forefoot and toes as progressive collateral occlusion occurs) or as "post-minor trauma" wounds since inadequate arterial flow proves ineffective to increased oxygen demands for cicatrization [34, 38]. Bed-ridden patients with PAD represent another high-risk category to develop pressure heel ischemic ulcers on preexisting vascular impairment [37, 38]. For this particular cohort exhibiting ischemic hind foot ulcers, current guidelines emphasize that prevention by scrupulous heel elevation or soft tissue contact interposition is mandatory [3, 28, 38].

The TASC II fundamental CLI criteria [3] as absolute ankle pressure (AP) inferior to 50–70 mm Hg, or diminished toe pressure (TP) below 30–50 mm Hg are unanimously accepted [3]. A series of parallel predisposing factors for ischemic tissue damage were evinced in the last decade. They either concern the arterial perfusion (tobacco use, dyslipidemia, hypertension, weight excess, hyperglycemia, hyperhomocysteinemia, etc.), or specific foot conditions (peripheral neuropathy, inflammation, edema, infection, bedridden status, hypoalbuminemia, hyperglycemia, uremia, cortisone therapy, etc.), all with huge influence on peripheral tissue regeneration [1–3, 27, 33–35, 37, 38]. Although arterial ulcers theoretically may appear anywhere on the ischemic limb [3, 33], the presence of multilevel CLI arterial disease inflicts

more distal localizations, particularly in subjects with deprived foot collateral reserve [1, 25, 29, 30].

Beyond common atherosclerotic arterial ulcers, other *arterial*-related ulcers were described such as superficial hypertensive wounds, peripheral embolic tissue defects (owning 0.01–0.2 mm. cholesterol particles), those associated with connective tissue arteritis, those affecting hypercoagulable states, or following microangiopathic lesions, within parallel to mixed nutritional, hemolytic, or neurologic disorders [33, 34, 36].

4.3. What determines ischemic tissue defects to slide toward chronicity and necrosis? Is there a conjuring threshold to consider?

It has been showed that in healthy individuals, peripheral wounds promptly tend to recover owning adapted cell's metabolism, appropriate oxygen supply, essential growth factors, cytokines, and matrix proteins inflow (Section 5.1.2.) that all endeavor to orient local tissue damage on "steady" sequential healing process [27, 33, 36].

Since initial ischemic changes last beyond local individual compensatory reserves [30, 35], the readapting mechanisms are gradually exhausted and local tissue homeostasis finally drifts toward biological extinction [36, 39, 40]. Inasmuch CLI wound onset may be commonly displayed over days or weeks [3], local infection and collateral depletion by septic thrombosis can urge irrecoverable tissue loss appearance and make it devastating [30, 32, 35]. Probably the real "tipping point" between viable or perished, for every inch of ischemic tissue around the wound relies on local collateral adaptation vigor [39]. Alike other ischemic models described in human tissues (stroke, myocardial infarction), the extent of necrosis core depends on rescue capacity inside the "penumbra" or intermediary neighboring zone [35]. For this transitional layer of undecided viability, a few factors strongly influence its fate. The timing and intensity of main ischemic threat, the type of arterial pathology, the remnant upstream arterial trunks and collaterals, and the elapsed interval to prompt debridement and revascularization, play a pivotal role in any arterial ulcer progress [30, 33, 36, 40].

Daily vascular practice proves that interventionists are more likely confronted with patients exhibiting more than one *long acting* adverse factors for tissue healing [39, 40]. These conditions can be summarized as malnutrition and hypoalbuminemia, lack of compensatory arterial collateral network, diminished arterio- and angiogenesis, peripheral edemas enhancing local compartmental syndromes, low cardiac output, and prolonged bony prominences pressure that collectively contribute as notable interferences in physiological cicatrization [34, 35, 37, 40].

4.4. Current CLI diagnostic: can we effectively assess the real ischemic burden?

A series of high-performance technologies conceived to assess tissue-related arterial disease were introduced in the last two decades. These methods afford high or low invasiveness and focus on different targets in evaluating CLI hemodynamic and tissue changes [29, 30]. With each passing year, novel or modernized diagnostic techniques strive for accurately scoring the degree of perfusion tissue impairment in mixed series of patients and arterial pathologies [1, 2, 27–32].

It has been showed that first *detailed clinical assessment* of each tissue defect is mandatory in all presentations [36, 38, 39, 40]. Basic characteristics of each ulcer (surface and depth), its precise location(s), and the appended inflammatory extensions before and after revascularization should be carefully analyzed and scored by trained clinical teams [38, 39].

The majority of available diagnostic techniques can be roughly divided into *macro-* and *microcirculatory* investigation tools. Some "routine" *noninvasive macro-vascular exams* such as the ankle-brachial index (ABI < 0.5, severe ischemia), the toe-brachial index (TBI < 0.7, presence of PAD), the ankle and toe pressure (<40 mm Hg, threat of the limb), the exercise stress testing, and the Doppler and Duplex assessments are well-documented and own undeniable benefits, and drawbacks [33–35, 37, 39]. Meticulous Doppler evaluation avails real usefulness for knowledgeable clinicians in determining antegrade versus retrograde tibial, pedal, or collateral flow toward the wound zone [24, 39]. It may also yield helpful information over the remnant "large caliber" collaterals in the targeted foot ischemic area [24, 35, 39]. A precise mapping of lower limb arteries specifying eventual stenosis, occlusions, and secondary collateral flow represents a valuable *preoperative* or *follow-up* guide for any interventionist in planning wound-directed revascularization [39].

Other low-invasiveness techniques for detecting "large" arteries and collaterals include last-generation multislice computed tomographic angiography (CTA with "Dual energy") and the magnetic resonance angiography (MRA adding "BOLD sequences") [33, 39]. The "Dual energy" CTA imaging represents a current evaluation method in our team experience for patients with normal renal function. This technology allows accurate calcific plaques removal in tibial and foot vessels and provides a true BTK "lumenograms" in these patients [39].

Despite notable progress in both techniques, these two methods host similar iodine or gadolinium-based contrast disadvantages, being contraindicated in allergic patients or for those suffering from chronic renal insufficiency [33, 39].

Unfortunately, in the daily clinical practice, most of diabetic or renal CLI patients with threatening foot ulcers often associate advanced nephropathy that challenges the use of Iodine or Gadolinium contrast agents.

Probably the most accustomed *macro-circulatory* yet *invasive* available test is represented by the digital subtraction arteriography (DSA) of the inferior limb arteries [1, 3, 28, 38].

DSA is currently recognized as a "key exam" in accurate ischemic flow assessment and classification [1–3, 38, 39]. It is cited to afford best available spatial resolution required to establish main arterial trunks and collaterals (>500 μm diameter) morphological details toward the wound zone [1, 3, 27, 35, 38]. DSA also enables appropriate diagnostic for eventual anatomical variables and their collateral network in each specific arterial pattern [1, 27, 35]. This *quantitative* information becomes essential in understanding individual vascular anatomy for performing eventual *direct* (wound targeted) or *indirect* (collateral supported) arterial revascularization to the wound zone [24–26, 39]. Peripheral angiography consequently helps in determining the most appropriate and "feasible" target vessel to be treated [23–26, 35].

It is shown that DSA affords the interventionist valuable *qualitative* information about *the severity* of distal leg ischemia (the "desert" foot presentation). It also provides accurate

characteristics of run-off vessels, the integrity of foot arches, and clues about potential technical difficulties in long chronic total occlusions (CTO) recanalization (the presence of concave/convex atherosclerotic caps) [1, 21, 29, 39]. This technology provides corresponding information about extensive calcifications, tortuosities, and available arterial-arterial communicants or "blush" irrigation around the ulcer's zone [25, 26, 31, 35, 39]. Inasmuch DSA bears evoked drawbacks due to iodine contrast (allergic or renal failure reactions), it also carries the eventual access-related risk for hemorrhagic complications (0.8–3% of cases) [27, 33, 39].

Modern wound practitioners equally avail latest *micro-vascular noninvasive* diagnostic technology, with soaring applications in the last two decades. Among these methods, some showed promising results such as the consecrated transcutaneous oxygen pressure [1–3, 33, 39]; the novel vascular optical tomographic imaging (VOTI) [41]; the "real-time" Laser-Doppler skin perfusion pressure [33, 35, 39]; the continuous tissue oxygen saturation foot-mapping (StO_2); and the recent ^{99m}Tc Scintigraphic, the PET, and the single-photon emission computed tomography (SPECT) scans (owning specific CLI 3-D detection at molecular level) [35, 39]. Parallel *microcirculatory* yet, more *invasive* exploration was recently documented gathering intraoperative "Indocyanine green" angiography (ICGA) [42, 43], the "Indigo Carmine" angiography [44], and the foot "micro-oxygen sensors" (MOXYs) technology, all with encouraging applications during wound-targeted revascularization [45].

4.5. The CLI multimodal approach: a novel contemporary concern

Bell et al. first proposed the notion of critical limb ischemia in 1982 for defining severe arterial flow deprivation that currently inflicts major limb amputation threat [46]. In their original publication, the authors characterize CLI essentially on *macro-vascular hemodynamic criteria*, such as the measured AP <40 mm Hg in the presence of rest pain and <60 mm Hg when tissue necrosis is noted [46]. It should be mentioned that in the original form of this concept, the diabetic group of CLI patients was deliberately excluded since neuropathy and infection are often associated and make more complex real ischemic stratification [46]. During the next 30 years, the term of CLI was broadly, yet most of the times inappropriately, used [29–32, 47] as to characterize a much larger hierarchy of severe arterial presentations, including diabetic and renal subjects [27, 30, 46–49]. Although the particular threshold from "reversible" to "irrecoverable" limb ischemia still dwells imprecise [27, 29, 31, 34], it is accepted that CLI often implies a poor limb outcome without prompt revascularization [1–3, 27, 30, 46, 47]. An eloquent 1527 CLI subjects review analysis recently performed by Abu Dabrh et al. on the natural history of untreated "severe" or "critical" ischemic limbs revealed 22% all-cause mortality, 22% major amputation, and 35% worsening in wound evolution rates at 1 year [48]. The almost similar observation was reported in 2016 by Vallabhaneni et al. in a 443 CLI cohort assembling more than 60% diabetics and 20% dialyzed patients [49]. They found 32 and 56% mortality rate at 1 and 3 years, respectively, and 24 and 31% major amputation rates at the same time intervals [49]. The authors conclude that not all patients were encompassing current ABI- and TBI-accepted CLI *macro-vascular* criteria, obviously are at high risk for major amputation [49].

We know nowadays that CLI associates a modest quality of life to the high rate of major amputations and that about 60% of mortality is documented between 3 and 5 years following the initial diagnostic [1–3, 32, 46, 47–49].

Parallel papers focusing on equivalent *macro-vascular* hemodynamic standards (ABI, TBI, AP, TP, etc.), equally fail to explain this huge heterogeneity encountered in CLI "limb salvage" and dedicated treatments [47–49]. Struggling to provide more accurate CLI categorization, several conspicuous classifications systems were proposed in the last two decades [1, 3, 30, 47].

Owning the Bollinger angiographic scale [50], the Trans-Atlantic Inter-Society initial Consensus (TASC I and II) [3, 51], the Rutherford staging of PAD [52], and the European recommendations for CLI management [53], complementary definitions yet adding only $TcPO_2$ *microcirculatory* references were settled [27, 47, 53].

In the recent years, novel PAD classification systems were developed alike the Graziani morphologic arteriographic indexation in diabetics [54], the Toursarkissian angiographic scoring for distal limb salvage bypass [55], and the "Jenali" tibial run-off classification system, with appended below-the-knee intervention protocol [56]. This latest is based on three grades for main infragenicular arterial trunks fluency associating three levels of time-related collaterally filling (at 3–6–9 s) [56].

Undoubtedly, all abovementioned iconographic scoring systems excel in meticulous angiographic anatomy analysis, yet only partially address concomitant wound index or baseline *microcirculatory* perfusion status [30, 39].

Despite real efforts in stratifying CLI intimate mechanisms, to date, all evoked classifications add a little emphasis on coupled *macro-* and *microcirculatory* evaluation, including individual wound characteristics [30, 39].

They also fail to quantify eventual threshold [47] below which inferior limb perfusion becomes nonviable without opportune revascularization [27–30, 47]. The risk of developing CLI and ischemic wounds seems considerably increased in diabetic patients, although prone to more frequently endure systemic ischemic events compared to general population [3, 27, 31].

Contemporary clinical expertise allows better knowledge over the multifaceted "Diabetic Foot Syndrome" (DFS) presentation that gathers arteriopathy, neuropathy, sepsis, pressure injuries, and cellular and molecular metabolic disturbances, in myriads of different clinical archetypes [31, 57]. A vehement need for more specific CLI delineation in these patients was increasingly recollected in modern vascular literature.

4.6. Does healing process in diabetics follow same predictable "standards" alike other CLI patients?

Soaring progress in arterial ulcers treatment is however confronted with an exponentially increasing number of diabetic CLI subjects each year [1, 31]. To date, the prevalence of purely neuropathic, ischemic, and combined neuro-ischemic foot ulcers in patients with diabetes was estimated at 35, 15, and 50% rates, respectively [57–59].

Reported DFS singularities include (1) the regular tibial trunks *calcifications* [2, 30, 31, 57] that match the extent of local neuropathy [25, 31], (2) the "end-artery occlusive disease" (EAOD) concept [59], (3) an impaired *arterio-* and *angiogenesis* [60], (4) a specific *collateral deprivation* following chronic inflammation and septic thrombosis of small vessels [31, 35, 57–59], (5) intrinsic vascular or *matrix impaired regeneration* [61], and (6) characteristic neuro-ischemic *compartmental hyper pressure* foot syndromes [62].

The EAOD theory emphasizes that in the collateral-depleted diabetic limb, "each millimeter of skin" up to the "entire foot" may rely upon one particular artery with *terminal* distribution [59], while this valuable vessel may be auspiciously targeted by "wound directed" revascularization, according to the angiosome concept [24–26].

Modern diabetic ulcer understanding builds a complete design of multifaceted and potentially devastating CLI effects in these patients [2, 31, 57–62].

Enthralling scientific works in the last decade evoke a possible central mechanism playing a pivotal role in different DFS pathological changes [59, 63]. Thus, chronic hyperglycemia may enhance at the mitochondrial-level expanded free radicals production, altering normal metabolic and cellular activity [63]. This malfunction affects more particularly normal regeneration at the *microcirculatory* level (vasa-vasorum and vasa-nervorum) also the tissue binding matrix [58, 59–61].

Arteriopathy and neuropathy, albeit regular DFS features (in different proportions) [58, 59], may probably share the same pathological emergence in the vast diabetic complications puzzle [57–59, 63].

Trying to stratify main DFS characteristics, a few classification systems were proposed. It should be mentioned the "Wagner" stratification [64], the PEDIS (perfusion, extent/size, depth/tissue loss, infection, sensation/neuropathy) [65], the University of Texas (UT) [66], the sepsis, arteriopathy, denervation (SAD) scale [67], the diabetic ulcer severity score (DUSS) [68], the multiple ulceration, wound area, pedal pulse, and ulcer duration (MAID) classification [69], and the "St. Elian wound score system" [70], rejoicing unanimously recognized popularity and documented clinical benefits [57–59].

However, most of these classifications fail to provide concomitant *perfusion* information [35, 47]; individual *ulcer features* [47]; *infection, denervation*, or *gangrene* specifications [47]; systemic factors report [2, 30] (Section 4.5); and healing prognosis [2, 40, 47]. All these clinical entities seem to bear a huge interest in healing evaluation [2, 31, 37, 39].

In same effort to fully perceive each DFS presentation, the remarkable WIfI classification [47] recently brought together Wound grades, Ischemia levels, and foot Infection ranked in a unitary view, as important variables for appended wound prognosis [47]. However, diabetic neuropathy [36, 58, 71] and concurrent systemic variables influencing tissue recovery [57, 61, 72] are not included in this model of examination. In a parallel analysis, owing a consecutive 249 CLI wounds series, Azuma et al. [72] found that beyond diabetes (including neuropathy and infection), equally end-stage renal disease (ESRD), Rutherford category 6 (including or not the heel), and low albumin levels, represented significant factors in the complex tissue recovery cascade beyond prompt revascularization [72].

5. Contemporary landmarks in ischemic wounds revascularization

Expanding clinical evidence in the last three decades supports both bypass and the endovascular techniques as useful strategies in CLI revascularization [1–3, 29–31]. Providing low invasiveness, high reproducibility, and comparable limb salvage rate to open surgery [21–73], transcatheter strategies continue to evolve with new low-profile and high-performance devices in arterial reconstruction [21, 29, 74]. For most "high-risk" CLI patients [1, 2, 31, 34], new endovascular approaches and techniques were designed. In succinct overview, the "drilling," the "subintimal," or the "parallel wire" techniques via the ante- or retrograde accesses, the pedal-plantar "loop," and the femoral-femoral or transtibial collaterals angioplasties were recently described [29, 74, 75].

Not with standing with these spectacular transcatheter performances, the "classical" bypass for distal leg reperfusion is still imposed as a fundamental technique for CLI diabetic foot revascularization, tissue healing, and limb preservation [1, 3, 72, 76]. High-skill distal vein bypasses to the tibial [72], to the pedal [77], and up to the plantar or tarsal foot arteries [78] equally by targeting remote branches of pedal arteries in some particular cases [1, 76] were successfully documented. We now know that both surgical and endovascular techniques are more likely complementary than competitive techniques since each of them holds major advantages and inherent drawbacks [1, 29, 30, 79]. Endovascular techniques essentially provide minimal invasiveness, great accessibility, and reproducibility for one or multiple below-the-knee CTO recanalizations [1, 29, 73–75]. Alternatively, bypass offers a higher pressure on targeted arteries and more physiological and pulsatile flow inside collaterals around the wound zone [35, 53, 77–79]. This particularity heightens arterial-arterial collateral shear stress and enhances rising arteriogenesis [58–60] toward further tissue cicatrization [1, 29, 35, 60, 72].

Although still heterogeneously structured [1, 73, 79], increasing contemporary clinical observation documents equivalent limb salvage, clinical success, and survival outcomes for bypass versus endoluminal interventions in selected groups of CLI patients [1–3, 27, 29–31, 79, 80]. Notwithstanding with initial historical considerations [79], these two strategies appear nowadays more intricate than ever inside the conceptualized "team approach" as CLI treatment [29, 35].

Parallel advances concerning the DFS revascularization and ischemic wound healing were equally testified in the last two decades [1, 2, 75]. Beyond striking surgical arterial reconstructions [76–79], new tapered nitinol [81], drug-eluting stents (DES) [82], and original drug-eluting balloon, (DEB) [83] were imagined. Novel or redesigned directional or rotational atherectomy devices [84], together with latest "bioresorbable scaffolds" technologies [85], represent few additional of numerous achievements that challenge today ancient technical barriers [1, 29, 75, 81–86].

6. New strategies for "wound targeted revascularization"

The complex cascade of tissue regeneration needs precise circumstances to unfold [85]. Beyond high-performance techniques in reconstructing arterial flow [72–86], new strategies about "when" and "where" to perform appropriate revascularization emerge today [1, 27, 30, 35]. Contemporary practitioners equally avail key data on the molecular mechanisms generating ischemic threat and tissue regeneration [59–61]. This knowledge, part of a larger "integrated multidisciplinary medicine" [87, 88], supports new strategies in limb salvage [1, 29, 48] based on precise arterial flow mapping [23–26] and deliberate tissue healing reengineering [29–31]. A new conceptualization of ischemic wound treatment rises at present [1, 2, 33], with promising serviceableness in patient's stratification [47, 53, 57, 59], revascularization selection [35, 38], and dedicated postoperative follow-up [31].

According to this modern emphasis, novel "hybrid" surgical and endovascular techniques [89], synchronous ante- and retrograde arterial accesses [74, 90], and novel topographic "wound-directed" revascularization (WDR) [24, 35, 91–93] proved useful to save more limbs for major amputation. Alternatively, extreme venous limb arterialization [94, 95] and cell stem treatment [1, 29] parallel to rising "multidisciplinary team" practice [57, 87, 88] have also been developed and seem to revolutionize previous CLI paradigms of care [1, 29, 92–94].

6.1. The "angiosome concept" in ischemic wound healing: a succinct overview

Among all innovative strategies in CLI wound treatment, a remarkable leap was undoubtedly marked by *topographic*, or intentional, *wound directed* arterial reconstruction [23–26, 35, 72, 91–93]. This theory represents a unique clinical application of the *angiosome concept* initially pioneered in 1987 by Taylor et al. in the plastic reconstructive surgery field [23].

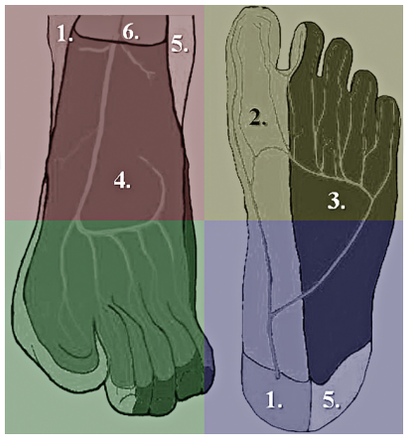

Figure 1. A schematic anatomic representation of the six angiosomes of the lower leg in a forefoot/hindfoot topographic view. (**1**) The *medial calcaneal* angiosome (from the posterior tibial artery). (**2**) The *medial plantar* angiosome (posterior tibial artery). (**3**) The *lateral plantar* angiosome (posterior tibial artery). (**4**) The *dorsalis pedis* angiosome (from the anterior tibial artery). (**5**) The *lateral calcaneal* angiosome (from the peroneal artery). (**6**) The *antero-lateral malleolar* angiosome (currently from the anterior tibial, also from the perforator branch of the peroneal artery).

The angiosome conceptualization describes more than 44 specific 3-D *tissue sectors* of the human body nourished by individual arterio-venous bundles called "the angiosomes" [23]. This anatomical representation was further referred to CLI treatment two decades later by Attinger et al. [24], owning encouraging clinical results.

The lower leg angiosome territories. The following skin and underlying tissue zones were earlier described as to nearly encompass six main *angiosomes* (**Figure 1**) of the foot and ankle [23–26, 91–93]:

- The *medial calcaneal* and appended *medial* and *lateral plantar* arteries angiosomes arising all from the *posterior tibial artery*. They supply the entire plantar heel and the medial and lateral plantar surface to the toes.
- The *dorsalis pedis* angiosome, downstream to the *anterior tibial artery* that nourishes the dorsal foot and toes areas, also ensures the upper and anterior peri-malleolar vascularization.
- The *lateral calcaneal artery* angiosome branching from the *peroneal artery* and that supplies the lateral, plantar heel.
- At a higher level of the superior ankle, other angiosomes were described, such as *the antero-lateral malleolar* owning its correspondent *antero-medial malleolar* angiosomes (both from the *anterior tibial artery*), and the *pstero-medial malleolar* angiosome following correspondent branch from the *posterior tibial artery*, respectively [23–26, 91–93].

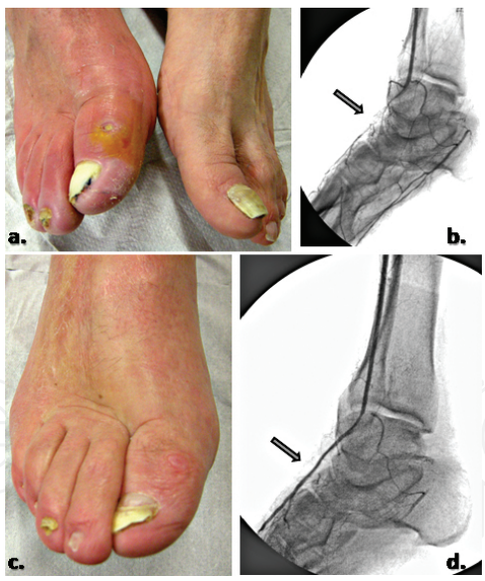

Figure 2. A diabetic neuro-ischemic ulcer associating cutaneous sepsis on the antero-medial aspect of the foot. (**a**) The initial clinical aspect (CLI, Rutherford 5). (**b**) The appended angiographic aspect showing complete occlusions of the dorsalis pedis and distal posterior tibial artery. (**c**) Healing aspect at three months, following (**d**) angiosome-targeted revascularization by deliberately opening the dorsalis pedis artery territory (arrow).

These vascular territories are closely interconnected by numerous *arterial-arterial* communicants [23, 24], whose caliber and density are strongly influenced by the age of patients, by each region's anatomy and by the manifest arterial disease triggering CLI [24, 35, 72, 96–98]. Every

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individual collateral system essentially assists blood supply between neighboring angiosomes. These compensatory branches the so-called "choke vessels" include *large-*, *middle-*, and *small-*sized arterial-arterial communicants, beyond the arterioles and capillary vessels in a vast "compensatory arterial foot network" [24, 29, 35]. All collateral interconnections between adjacent angiosomes are submitted to specific hemodynamic influences related to local *arterio*genesis and *angio*genesis processes [35, 59, 60].

The angiosome clinical model implies a conspicuous vascular anatomical order, although subject to specific pathophysiological changes in every CLI individual pattern. Optimal *wound-targeted revascularization* probably means correct angiosome-related anatomical evaluation associated with individual collateral-related pathophysiological judgment for each CLI presentation [30].

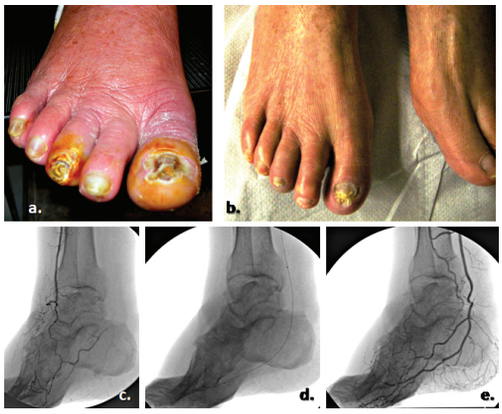

Figure 3. Wound-targeted revascularization for severe forefoot sepsis and tissue necrosis, extending to the plantar side of the hallux and toes. (**a**) The initial clinical aspect (CLI, Rutherford 5). (**b**) Healing after topographic revascularization and multidisciplinary team care at five months. (**c**) The starting angiographic image showing complete posterior tibial artery occlusion (the dominant wound territory), and the dorsalis pedis thrombosis. We can remark only a few remnant collaterals (the characteristic diabetic foot collateral deprivation) represented by two lasting diagonal arteries. (**d**) Endovascular plantar angiosomes-targeted revascularization by posterior tibial artery intentional reopening. (**e**) The end-procedural result showing the posterior tibial, the plantar arteries, and the plantar arch reperfusion in an intentional wound-directed revascularization.

In young subjects with unaltered collateral network possible post-traumatic or ischemic injuries activate unmitigated "choke-vessels" that warrant (at some point) effective compensatory blood pressure between adjacent angiosomes [24, 39, 96, 97]. Atherosclerotic, inflammatory, or local thrombotic conditions may alter this unique natural compensatory system. As previously described [23, 24], the foot angiosomes are 3-D dynamic and continuously interacting structures [30]. Although their primary anatomical distribution seems accurately reproduced in more than 90% of subjects (owing 6–9% eventual anatomival variants) [23, 24, 26, 91], their interconnections ("choke vessels") are yet submitted to continuous changes, according to each type of CLI pathology [72, 95–98].

Assessing and treating ischemic wounds in the light of the angiosome theory imposes a flexible reflection upon *how* utilizing the remnant arterial-arterial connections (**Figures 2** and **3**) at best flow benefit for the patient [88, 97].

6.2. What group of ischemic ulcers may need WDR?

Inasmuch genetic collateral network warrants a remarkable "rescue system" in non-atherosclerotic patients, it can be dramatically hindered in specific diabetic or uremic ischemic wounds [24, 35, 72, 96–98]. The interventionist should be aware of treating peculiar diabetic and ESRD *ischemic ulcers*, for that these patients may hide huge collateral decay and poor arterial-arterial connections among adjacent foot angiosomes [72, 97]. Eventual *indirect* [26] or *nonspecific* revascularization [25, 93] in these subjects may fail to afford correct arterial flow to the wound by a lack of collateral resources [25, 59, 72, 96].

Alternatively, the use of WDR principle in these cases seems to provide improved healing results [24, 39, 72, 96–98] owning scrupulous *macro-* and *microcirculatory* evaluation, planning for intervention and follow-up [39, 96, 97].

Despite encouraging tissue healing and limb salvage results for both, bypass and endovascular treatment [24–26, 91–93], uncertainty still dwells concerning the utility of angiosome-oriented revascularization in specific CLI groups of patients dysplaying different etiologies of arterial disease [35, 72, 96, 97]. Growing clinical expertise, however, seems to support WDR in "low-collateral" CLI patients such as those presenting DFS (**Figures 2** and **3**), or ESRD ischemic wounds [72, 91–93, 96–98].

6.3. Does topographic WDR allow unrestricted anatomical applications?

The angiosome-oriented revascularization theoretically offers superior chances for healing in selected ischemic wounds, yet this theory still awaits for further prospective validation in larger groups of equivalent CLI patients [92, 97].

Lower limb topographic anatomy addressed to date unnumbered ex vivo or clinical works [99–102] (most of them in the last 50 years) and their analysis largely overpasses the purposes of this chapter. However, some compelling points should be probably mentioned for better picturing this impressive graduation in the distribution of the arterial tree toward the target tissue [35, 101, 102]. The whole body vasculature can be delineated from a "fractal" point of view, as harmonious repetitive patterns of peripheral tissue irrigation [35, 101]. Particularly concerning the inferior limb vascularization, this archetype evinces some specific *levels of irrigation* [35]. A primary *level I* of perfusion contains the main arterial and venous bundles (i.e. iliac and common femoral), the *level II* gathers first rank arterial branches in the thigh and calf (i.e. the superficial and profonda femoris and the three tibial trunks), and the next *level III* features distinct ramifications for *specific skin and underlying tissue zones* in the foot [35]. This level also encompasses the *large* collaterals (around 1 mm diameter), including *the angiosomes branches*, the appended *foot arches*, and the *metatarsal perforators* [24, 35, 101], yielding specific interest in topographic revascularization [23–26, 35, 93, 100]. The next *level IV* holds the *medium-* and *small*-size (<0.5 mm) collaterals, while next microcirculatory ranks assemble *level V* that gathers *the arterioles* and the *level VI* connecting the *capillary* tier (around 8-μm diameter) [39, 101, 103]. This latest convenes several millions of small micrometric conduits in the whole human body, approximating 60,000 miles of estimated length [102].

Another parallel and more common anatomical partition used in CLI literature roughly distinguishes the *macrocirculatory* rank (that embodies previous *levels I–IV*) from the *microcirculatory* level (equivalent to other *levels V* and *VI*) of limb perfusion [1, 27, 29, 30, 103–106]. By bridging these two levels, the *medium* and *small* muscular arteries and adjacent *arterioles* contribute to a continuous *pacing system* of local tissular perfusion [103–105]. Since CLI threat appears, this function seems to be notably distorted until focused revascularization is applied [25, 60, 106].

According to the above considerations, several anatomical variants were equally described, mainly concerning level III of limb flow distribution [104, 105]. Following two recent meta-analysis gathering 7671 [107] or 5790 inferior limbs [108], and two "in vivo" analogous angiographic observations [109, 110], *native atypical leg arteries* were described in utmost 7.9–10% individuals out of general population [107–110]. Among these variants, hypoplastic or aplastic posterior tibial artery was encountered in 3.3% cases, whereas the anterior tibial trunk was absent in about 1.5% of instances [108]. The presence of highly emergent anterior tibial artery or irregular tibial trifurcation was described in 5.6–6% cases [109–110], while anomalous origins of the dorsalis pedis artery were encountered in 4.3–6% presentations [109, 111]. Aberrant first dorsal metatarsal artery and appended first toe dominant irrigation was described in 8.1% cases [112], parallel variants of the arcuate artery in 5% [113], and modified courses of the plantar arch and plantar arteries in 5% of presentations [114]. The intimate knowledge of these variants seems significant for the advised interventionist since *wound-directed revascularization* is planned [30, 100]. The presence of one anatomical popliteal variation (i.e. high origin of the anterior tibial trunk) on one side may indicate possible ipsilateral foot vessel abnormalities in about 21% of cases [107, 109], and similar contralateral leg variants in 48% of instances [109, 110]. Concomitant *acquired arterial flow disturbances* were also cited in lower leg ischemic presentations, most of them accompanying the diabetic neuro-ischemic foot syndrome [34, 53, 59]. The majority of these anomalies were represented by occlusions of at least two or all tibial arteries in more than 70% of CLI diabetic subjects [110, 115]. A higher prevalence of long (>15 cm) obstructions in the posterior tibial and plantar arteries [25, 116, 117] and extensive (type II) calcifications [25, 91] in most diabetic calf and foot arterial segments were also demonstrated [91]. Our group experience over 232 diabetic CLI limbs [91] with Wagner grade 2–4 foot wounds [64] availing *angiosome-targeted* revascularization [24, 96–98], also confirmed more frequent posterior tibial atherosclerotic occlusive disease (68% of cases versus 25% anterior tibial and 7% peroneal presentations) [91]. Moreover, the posterior tibial hypoperfusion showed significant (>90%) concordance with distinct plantar, heel and forefoot (on the plantar side) skin, and adjacent tissue trophic lesions [25–91].

Although precise below-the-knee arterial *anatomical knowledge* is of paramount importance in planning "angiosome-directed" revascularization [91–93], the skilled interventionist should also corroborate additional *hemodynamic information* enabled by each collateral pattern [24, 93, 96–98, 118].

Even in the presence of unusual anatomical variants to supply the foot, topographic revascularization still appears feasible [39] by taking advantage either on visible or on unmasked

arterial branches (the "dormant" collaterals) that gradually reveal during CTO recanalization [24, 35, 56].

It becomes clearer that since all tibial trunks become occluded, the tipping point between hypoxic tissue regeneration versus chronic ulceration and necrosis hinges upon *the remnant individual collateral reserve* and ways to deliberately use it in addressing the ischemic threat [24, 30, 34, 59].

Despite encouraging results to date [91–93, 96], the angiosome concept may provide better, yet not complete, ischemic tissue control [35, 61, 72, 118].

Topographic WDR for ulcer healing remains an enthralling subject of discussion. Certainly, alike similar new openings of flourishing interest in tissue regeneration, the scarcer the available evidence, the acrider the current debate, mostly based on heterogeneous retrospective deliberations [35, 72, 92, 96–98, 118].

7. The state of foot collaterals: a key principle in modern CLI wound treatment

The TASC II recommendation [3] for prompt revascularization in CLI is generally accepted [1, 27], however, do all these interventions address similar extent of ischemic threat? Do all these interventions bear then, equivalent expectations for tissue recovery? [49] More concretely, does the modern vascular interventionist truly control all hemodynamic *macro-* and *microvascular* changes at the wound level while performing CLI revascularization? [49, 61, 97] Up-to-date research reveals that not all proven lower limb ischemic ulcers share the same TASC II/CLI criteria [3] and, consequently, harbor the corresponding amount of ischemic burden! [2, 31, 49, 61, 118, 119] Owning steady improvement in diagnostic and treatment, modern practitioners start to adapt current CLI standards to each type of arterial pathology [1, 35, 73, 107], and to resize ischemic ulcer appraisal in deeper *macro-* and *microcirculatory* perception [39, 59–61, 97, 106]. The contemporary medical community is now facing *a novel* challenge wherein specific strategies for revascularization in CLI patients *with* and *without* a convenient foot *collateral network* [92, 96–100, 119]. Thorough research in diabetic CLI treatment had already evinced good tissue cicatrization since topographic revascularization is performed in subjects having a poor collateral reserve [26, 92, 96–100, 119]. It is known that DFS currently alter common foot cutaneous, the underlying tissue and bony presentation, by iterative inflammation, scars, ischemic necrosis, sensorimotor neuropathy, and local pressure aggressions [57–60]. Even though that CLI/DFS severely distorts the "classically pictured" angiosomal foot vasculature [23–25, 96–98], *wound-targeted revascularization* using the *surviving collateral system* represents a valuable solution for better tissue regeneration [92, 96–100, 119].

Today's evidence suggests that both *macro-* and *microcirculation* evaluation should be routinely considered in each ischemic ulcer presentation toward deeper CLI understanding, as a whole limb circulatory pattern [39, 105].

7.1. Compensatory *collateral systems* relying the foot angiosomes and derived wound healing implications

An impressive compensatory collateral network interconnecting neighboring foot and ankle angiosomes was thoroughly documented by previous publications [23, 24, 101, 102], available as to counterbalance any possible ischemic threat [23, 24, 98].

The central *arterial-arterial* communicants relying upon different leg angiosomes encompass numerous *small* to *large* collaterals (the above-described *levels III and IV*), beyond the arterioles (*level V)* in a sequential model of perfusion [35, 101]. Numerous "large" foot collaterals hold particular importance in supplying adjacent angiosomes [24, 39, 118]. They also seem to play a pivotal role in intentional "wound-directed" revascularization and appropriate tissue regeneration [35, 96–98, 118]. These vessels assemble the *foot arches*, (acknowledging eventual 5–9% anatomical variations, Section 6.3) [108–114], the *metatarsal perforators*, the anterior *communicants*, and other sizable *arterial-arterial* branches such as the dorsal foot-to-plantar, or the peroneal-to-posterior tibial *rescue* heel collaterals (*level III* of perfusion) [35, 101].

In the same design, yet with narrow compensatory significance (Section 6.3), the *medium-* and *small*-sized muscular collateral arteries (*level IV*) [35] and *the arterioles* (*level V*), also contribute in vital tissue flow preservation [103, 105, 106]. These "rescue" connections were also implicated in the "initiatory" phase of revascularization (Section 4.1) [35, 105] and actively partake throughout the vast "choke vessels" salvage system [23, 24], before or during the angio- and arteriogenesis processes [104–106]. Regardless individual variations, the following groups of arterial-arterial collateral connections were appointed in CLI flow compensation [24, 35, 39, 102, 118]:

- The communications between the posterior tibial and peroneal arteries (via the *medial* and *lateral calcaneal branches*, also via the *posterior peroneal branch*) play an important role in *ischemic heel ulcers* supply, equally for targeted hind foot or heel intentional revascularization [24, 72, 96–98].

- The connections between the *anterior* (dorsalis pedis) and the *posterior tibial* (plantar) arteries. These branches ensure either directly via diagonal arteries or following the first *metatarsal perforators* or through the metatarsal *paired anterior* and *posterior inter-digital collaterals*, a significant compensation in *forefoot* and *toes ischemic tissue* flow preservation and eventual tarsal/metatarsal reperfusion [24, 35].

- The arterial compensation around the *peri-malleolar wounds* is reinforced by the *lateral peri-malleolar anastomoses* linking the peroneal artery (via the *anterior perforating branch*) with the anterior tibial trunk (via the *antero-lateral malleolar branch*). Following similar, but more medial connections, *the medial peri-malleolar network* (sharing similar *medial malleolar branches* from the anterior and posterior tibial arteries) represent complementarily, yet distinct, pathways for blood compensation in the ankle [24, 35].

- The communicants between *both plantar arteries* (medial and lateral, from the posterior tibial artery) and the *lateral and medial tarsal arteries* (via the anterior tibial artery) seem to enable influential compensatory flow to eventual *plantar ischemic wounds* [24, 35, 39].

All these briefly schematized *arterial-arterial* communications constitute but a small part of the whole natural foot compensatory system against ischemic aggression [23, 24, 35]. Although severely compromised in distinct CLI categories of patients (diabetes, ESRD, and inflammatory arteritis) [59–61, 104], all these "rescue branches" [35, 59, 101, 102] or "choke-vessels" [23, 24] provide noticeable flow assistance during miscellaneous ischemic injuries. Their appropriate evaluation affords valuable diagnostic and therapeutic knowledge for better tissue preservation and limb salvage [39, 56–59].

In this exhaustive "regional view" of ischemic tissue perfusion, albeit more precise than blunt angiographic assessment (Section 4.5), it appears that *not all foot areas may express similar ischemic affliction* [59–61, 104]. Even more surprisingly, the ulcer's area could not always stand for the lowest perfusion point in the ischemic limb, since severe neuropathy, inflammatory swelling, sepsis, and local skin trauma may add complementary hindrance to main CLI threat [26, 27, 31, 33].

Future diagnostic tools focusing on *superficial* and *deep* tissue "wound-oriented" arterial flow may eventually complete this unique holistic view of the neuro-ischemic diabetic foot [33, 39, 53, 59].

We know today that diabetic and renal CLI patients express serious tissue regeneration handicap, inflicted by specific infragenicular arterial collateral depletion [29–31]. This significant decay in tissue regeneration also appears proportionate with the *type* and *time* of ischemic suffering [1, 2, 27, 30, 59]. In this perspective, recent researchers advise reasonable adaptation of current revascularization indications upon individual *macro* [3, 41] and *microvascular* CLI characteristics [29–31, 39], weighted in patients *with* and *without* available collateral reserve [29, 39, 59].

8. The essential role of multidisciplinary approach in ischemic ulcer healing

Increasing clinical evidence suggests that despite "well-suited" revascularization efforts, at least 25% of DFS ulcers will eventually not heal, and around 28% may end however with some form of amputation [58, 120].

It appears unmistakable that no current *single* therapy can enhance *alone* profitable healing results in a majority of CLI ulcers [1, 27, 58] without concomitant management of all risk factors, including ischemic, metabolic, septic, local pressure, neuropathic, and adequate off-loading appointed treatment [1–3, 120–123]. Wound healing embodies a complex cascade of molecular and clinical events in continuous dynamic interaction [34, 48]. It was stated that because CLI wound etiology is always multidimensional [1, 27, 58], specific therapy in turns requires a parallel multidisciplinary application [1–3, 120, 121].

Every individual risk factor requires accurate identification and management and represents a fundamental task for any multidisciplinary wound center to encourage [124]. Investing

healing as the primary endpoint in care acts as a real benchmark for all collective therapeutic efforts [57, 87, 124].

The recent guidelines document of the Society for Vascular Surgery connecting with the American Podiatric Medical Association and the Society for Vascular Medicine acts as a great reference to current evidence of ischemic wound treatment [120]. This noteworthy analysis addresses best available proofs and guidelines to date on the following main indicators: (1) prevention of diabetic foot ulceration, (2) off-loading, (3) diagnosis of sepsis and foot osteomyelitis, (4) specific wound care, and (5) peripheral arterial disease in DFS [120].

Prevention following evidence-based program includes the patient and the referral General Practitioners (GP) as active members of the multidisciplinary group [120–123]. Knowing that peripheral neuropathy can generate about 45–65% of DFS ulcers, patients with neuropathy hold >3.5-fold complementary risk for iterative neuro-ischemic ulceration [26, 71, 87, 120]. Adequate *laboratory tests* surveillance also represents a critical method as to minimize detrimental obstacles in tissue regeneration [120–123]. It has been recorded that for every additional 1% increase in HbA_1C, there is a 0.028 cm/day healing decay in DFS wounds [120–125]. The major importance of *off-loading* devices in the global healing process is acknowledged [57, 58, 120–122]. Pressure reduction is reputed to allow superior healing effects to any revascularization strategy [2, 57, 58, 120–124]. Early diagnostic and treatment of *foot infection* also have paramount consequences in correct tissue regeneration [2, 57–59, 120–122]. Expeditious *local wound debridement* following timely reevaluation schedule bears huge implications for maintaining tissue viability, parallel to revascularization [57–59]. Since aggressively applied, early debridement can save millimeters of "time-dependent" irreversible damage [2, 57, 58, 61, 87, 120–124].

Appropriate *wound dressing* should help by maintaining a moist wound bed, providing exudate drainage, and urging granulation of tissue defect [53, 57, 120, 126].

The adapted dressing should match each specific CLI pathology, wound features and location, and individual amount of exudates, inflammation, and pain [87, 88, 120, 126].

New *complementary therapies* including negative pressure therapy, living cellular therapy, extracellular matrix products, and hyperbaric oxygen therapy were equally developed in the last years [57, 127]. Their application should follow multidisciplinary team advises [88, 120, 127] in ulcers that fail to demonstrate >50% area reduction per month, using standard therapy [120, 127].

Although revascularization still holds specific postoperative indicators [33, 39], the global efficacy of multidisciplinary approach can be timely rated by percentage reduction in wound extent as an early predictor of clinical success [120, 126]. Wound surface diminution of 10–15% per week, or >50% in 4 weeks strongly suggests increased likelihood of healing and diminished probability for amputation [120, 121, 126].

8.1. Ischemic wound healing as an integrated medicine concept

The contemporary practitioner becomes aware that every ischemic ulcer presentation should be carefully weighted and treated alike *distinct pathological prototype*. It appears reasonable that for every single ulcer puzzling (in various amounts) possible neuropathic, ischemic, hyperglycemic, uremic, venous hypoxic, septic, hypoproteic, or pressure threats, only a multimodal team approach may afford better healing expectations [121–126, 128, 129]. Every chronic ulceration case can be theoretically approached alike a 3-D graphical mold assembling in different proportions of some or the whole of the determinants mentioned above. The vital role of any multidisciplinary team is to decode each clinical presentation into basic pathological influences and treat them upon best available knowledge granted by all participant specialties [121, 123, 126].

9. Conclusions

In treating arterial ulcers it should be remembered that not all foot sectors share same ischemic affectation and that not all patients with comparable *macro*-vascular images bear same collateral reserve and related *micro*-vascular tissue recovery resources.

Contemporary research reveals astonishing multilevel anatomical and physiological intricacy of lower limb blood supply, viewed in a dynamic and time unfolding perspective. This apparent complexity represents but plausible challenges for the experienced interventionist availing high-performance macro and microcirculatory diagnostic and treatment methods for revascularization and tissue healing.

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