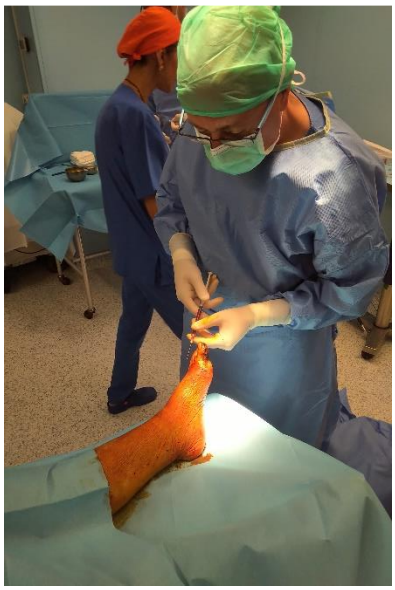
Regenerative Therapy with Autologous Mononuclear Cells from a simple sample for the treatment of the diabetic foot and ischemic skin lesions of the lower limb.

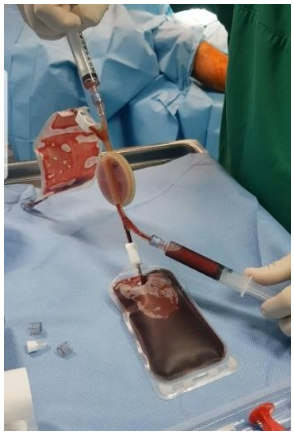
In atherosclerotic arterial vascular pathology, and in particular in the ischemic (poorly oxygenated) diabetic foot, ulcers and skin lesions in general occur because of a deficient vascularization due to the disease itself and other associated risk factors such as arterial hypertension, hypercholesterolemia and smoking. Cases are always on the rise as these diseases, like Diabetes Mellitus, are continually expanding. Ischemic lesions of the foot, as in the diabetic foot, are often disabling or lead to a more or less significant reduction in the patient's quality of life. Moreover, the response to recovery interventions varies depending on the severity of the problem, the anatomical damage and the age of the patient. However, the question arises from a common need: is it possible, in the different cases, to accelerate the process of tissue regeneration and promote functional recovery by reducing ischemic injury, wear and tear, and surgery? The answer is yes: through a new method, which is based on solid assumptions and an already consistent international medical literature, the regenerative treatment of soft tissues has shown more than flattering results. "It involves implanting autologous mononuclear cells from the peripheral blood, therefore belonging to the patient himself - explains Dr. Christian Baraldi, specialist in cardiac surgery and expert in vascular and endovascular surgery - through a cutting-edge technique that combines the most sophisticated methods with the simplicity of the treatment".

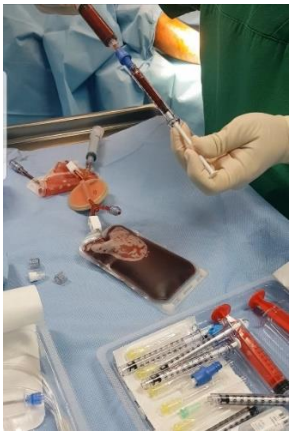
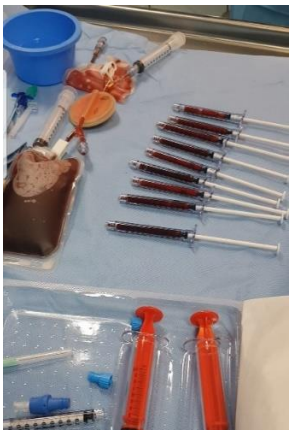


"Peripheral blood is taken from the patient from which, through a system that never allows the blood to come into contact with the outside, mononuclear cells (monocytes and lymphocytes, i.e. cells of the immune system) are filtered and concentrated. This cell concentrate is then injected into the chosen site. The Monocytes, once implanted, will differentiate into Macrophages".
Macrophages - the "scavengers" of the immune system - actually play a fundamental role in the process of tissue regeneration: when an ischemic lesion forms, chemical mediators and cells come into play. In fact, populations of macrophages are activated, initially M1

macrophages, which initially stimulate the inflammatory process (reaction to the harmful event), but at the same time enhancing the body's response to the insult and promoting the activation of M2 macrophages. The latter turn off the inflammatory process, modulate it and promote the transformation of mesenchymal cells (progenitor-stem cells), resident in the tissue, which arrive at the site of the "battle", resulting in the start of a correct and effective process of Physiological Regeneration, hence the term of the procedure "Regenerative Therapy".
Dr. Christian Baraldi explains: "Mesenchymal cells are undifferentiated pluripotent stem cells, which can meet various fates: remain as such or differentiate into cells of different tissues, thus promoting tissue regeneration. Upstream of the action of stem cells is therefore the activity of macrophages, which modulate, govern, activate, pilot the whole process that leads the undifferentiated mesenchymal cell to the cell of the regenerated tissue, promoting neovascularization".

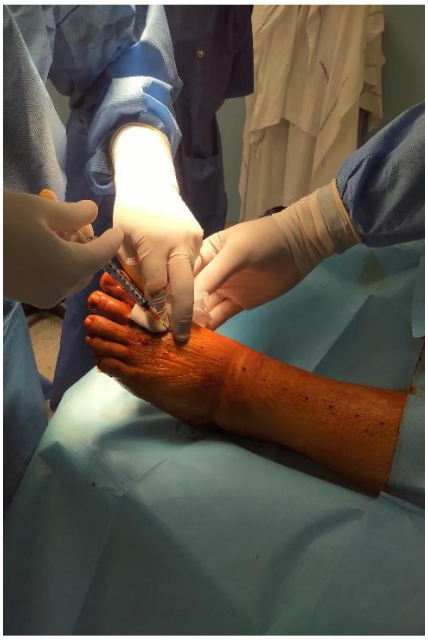
Dr. Christian Baraldi entrusts to images the explanation of the entire process, which follows the steps of the organism: "With this method we have implanted mononuclear cells - he says - and so the regeneration process will be more stable and durable. The implantation of autologous mononuclear cells from the peripheral blood is the future that is coming: several and relatively recent studies in the International Literature (2000s) support the absolute validity of the technique, which does not alter, and indeed promotes, the natural processes of healing/regeneration". When can it be used? "There are many tissues that can be regenerated, including vascular and dermal-epidermal. As mentioned, implantation of autologous mononuclear cells from peripheral blood can be used in critical lower extremity ischemia and the diabetic foot."
"In practice - describes Dr. Baraldi - it is as if we put a "turbo" in the tissue regeneration system, optimizing quality and quantity of the process. Contraindications constitute a limited list: no to the procedure in case of tumor pathologies. There are no theoretical age limits.



Recent studies (published in Nature Medicine by Stuart J Forbes and Nadia Rosenthal) - says Dr. Baraldi - have shown a new and unexpected role of the cells of the immune system that can promote healing by favoring the regeneration of an injured tissue with an initially unfavorable micro-environment, such as ischemic (poor oxygen).
Mononuclear cells from peripheral blood, referred to in the scientific literature as PB-MNC (Peripheral Blood Mononuclear Cells, consisting of the population of monocytes/macrophages and lymphocytes), represent - Dr. Baraldi said - an autologous cell concentrate with high angiogenic and regenerative capacity used today in the treatment of patients with critical limb ischemia that cannot be revascularized, or undergoing effective revascularization but with ulcerative skin lesions and in general in the treatment of diabetic foot.

"It has long been known that in the patient with obstructive artery disease physiologically two different forms of compensatory vascularization occur: angiogenesis and arteriogenesis. Angiogenesis refers to the development of a new capillary circulation from pre-existing capillaries in response to local tissue hypoxia (oxygen deficiency) and is mediated by the release of cytokines (VEGF and other cytokines). Arteriogenesis, on the other hand, also called collateral growth, is the transformation of pre-existing arterioles into functional collateral arteries, capable of compensating for reduced flow, through a significant increase in vessel caliber.
In arteriogenesis, the original diameter of a small arteriole can increase as much as 20-fold. It has also been reported, in addition to the increase in monocytes/macrophages also an increase in lymphocytes (thus of total PB-MNC, monocytes and lymphocytes) around the new collaterals indicating a fundamental importance of these cells in the growth of new vessels."
The physiological mechanism of compensation, of arteriogenesis, through the recruitment of monocytes and lymphocytes is not sufficient in some patients, as in the diabetic subject, probably also because of the low number of cells reaching the ischemic tissue itself.
Particularly interesting - adds Dr. Baraldi - is the correlation shown in several studies between risk factors of critical ischemia and low number of circulating mononuclear cells: in particular this mechanism is compromised in diabetic patients, smokers, with hyperlipidemia in which the concentration of these cells measured is strongly decreased.
Here it is clear the important role of regenerative therapy in bringing mononuclear cells from outside bypassing the blocked arteries that would prevent the arrival in the ischemic/injured site through the use of simple syringes.
Dr. Christian Baraldi is one of the few surgeons in Italy to perform in the vascular field, and in particular in the ischemia of the limb and diabetic foot, the Regenerative Therapy, obtaining amazing results in Calabria.

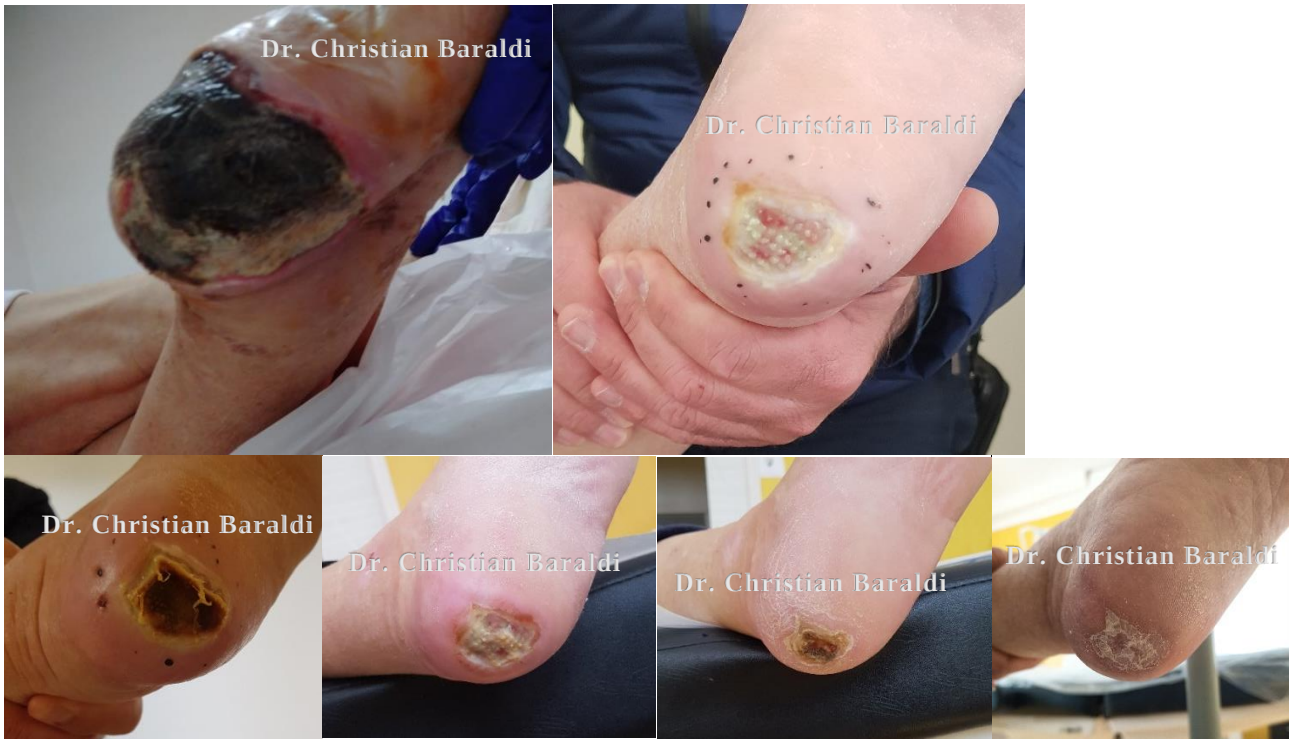

In conclusion we can therefore say, on indications given by recent studies, that:
- The immune system has a key and decisive role in tissue regeneration and in particular the monocyte/macrophage population;

- The immune system through peripheral blood mononuclear cells (PBMNC) controls and regulates the activity of stem cells themselves;
- Effective regenerative therapy must first control inflammation to create the ideal substrate for autologous cell concentrates because if a tissue is inflamed the regenerative capacity of mesenchymal stem cells (MSCs) is greatly reduced;
- The strong anti-inflammatory capacity (NFKB inhibition, polarization in M2) of monocytes/macrophages make them ideal candidates to physiologically control inflammation;
- Both monocytes/macrophages and lymphocytes have a marked angiogenic and arteriogenic action demonstrated in vitro, in vivo in animal model and by numerous clinical trials;
- The angiogenic activity of PBMNCs is increased by hypoxia (< oxygenation);
- Monocyte angiogenic activity is a physiological function: these are the cells that form the collaterals that are spontaneously created in ischemic tissue;
- Excessive activation of M1-resident macrophages with poor polarization in M2 has been described in various pathological situations such as unhealed lesions, diabetic foot;
- Effective regenerative cell therapies must have the ability to polarize in M2
- Implantation of monocytes taken from the peripheral circulation polarizes M1 inflammatory macrophages into M2 regenerative macrophages in unhealed lesions of diabetic patients.

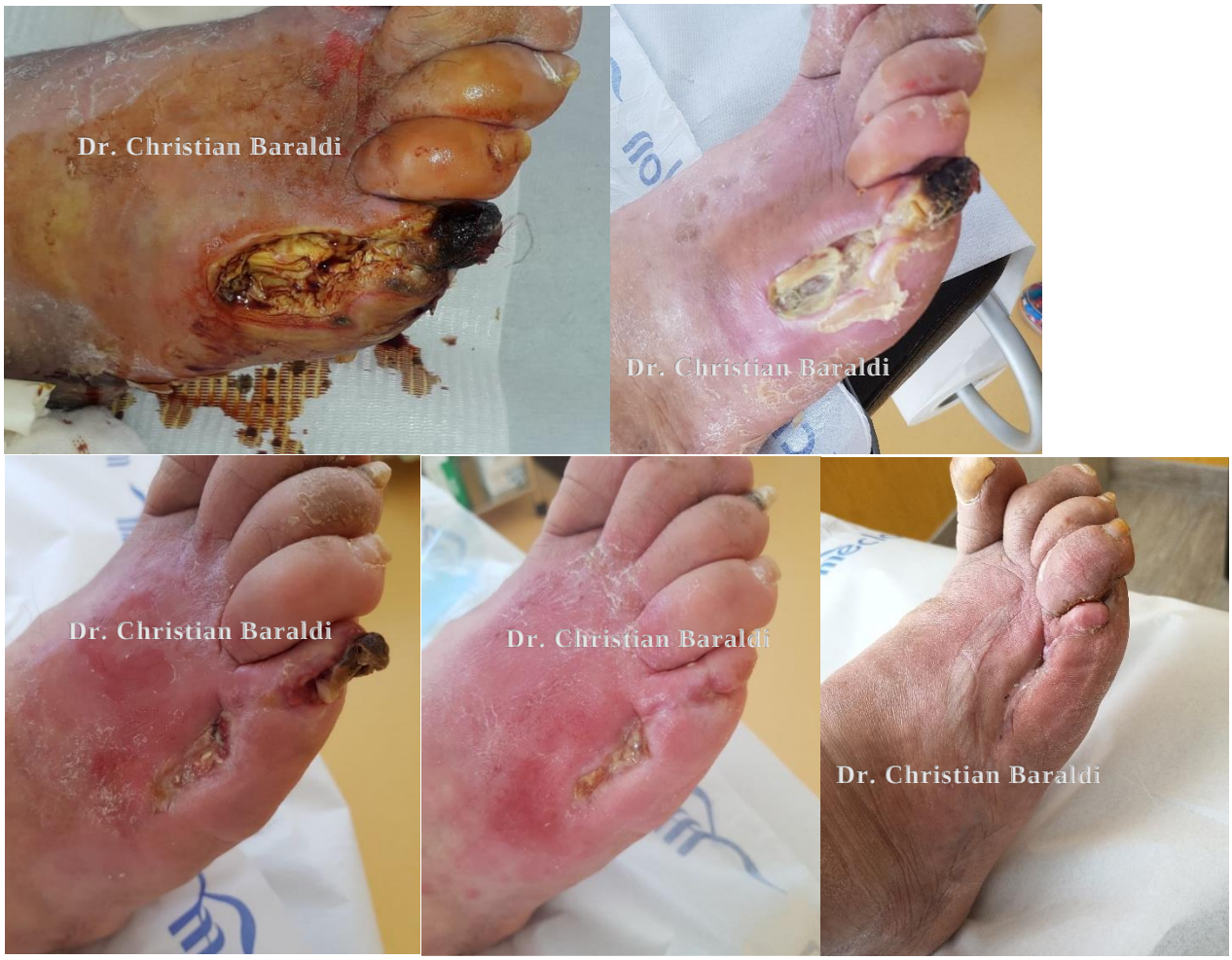
Numerous scientific evidences published in the literature indicate the implantation of MONONUCLEATE FROM PERIPHERAL BLOOD (monocytes/macrophages and lymphocytes) as a non-invasive, repeatable, safe and effective technique.

The results seem excellent based on my experience - says Dr. Baraldi - and not only. The scientific evidences are many and they already indicate the effectiveness of the method.
Two cases treated:

Patient 1



Patient 2: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