FREMS application in diabetic foot syndrome
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**Introduction:** Peripheral neuropathy is a frequent and disabling microvascular complication of both type 1 and type 2 diabetes. Diabetic Neuropathy affects up to 60–70% of diabetic patients and is the leading cause of foot ulceration and amputation. Improved blood glucose control reduces the risk of peripheral diabetic neuropathy (PDN), thereby implicating hyperglycemia as a leading causative factor. This condition may be prevented by good blood glucose control; however, it is at best halted, once established, even after long-term blood glucose normalization. The pathological hallmarks of diabetic neuropathy are microangiopathy of the vasa nervorum, loss of axons and axonal atrophy, all of which are the result of a combination of different mechanisms of tissue damage that are common to all long-term complications of diabetes.

The pharmacological treatment of diabetic neuropathy is largely unsatisfactory, mainly due to a lack of drugs that act on the underlying pathogenetic mechanisms. Aldose reductase inhibitors are among the few compounds with this mode of action; however, the results of clinical trials performed to date have been disappointing. Consequently, current therapy is purely symptomatic, aiming to relieve the pain associated with neuropathy through the administration of various analgesics, tricyclic antidepressants, anti-arrhythmics and, more recently, the new anti-epileptic agents gabapentin and lamotrigine and opioids.

One of the new and promising directions on the way to find an adequate solution to this problem is using Neuromdoulation devices in order to activate the inner structures of the neuro-vascular pathways. FREMS is a “biocompatible” electrical neuro-stimulation of recent generation. FREMS produces series of biphasic, asymmetric, electrically balanced pulses with a multiparametric modulation of the provided electrical signal. Series of impulses are continuously modulated in frequency, duration and time and this is the important difference between FREMS and others electrical stimulations like TENS. The sequences of impulses are conceived on the basis of the characteristics of the tissues to be enrolled, influencing subcutaneous functional structures. The result is the production of determined and repetitive events such as vasomotion, intended as the rhythmic pulsation of the vessels, through the involvement of the pre-capillary sphincter muscles of the microcirculation with two important demonstrated effects: the release of vascular endothelial growth factor and vasomotion (Bevilacqua et al., J.Endocrinol. Invest 2007; Conti M et al, J Diabetes Complications 2008). Based on these effects FREMS was applied to diabetic foot pathology were damage is at micro and macro-vascular level. At first FREMS’effects were
investigated in painful neuropathy associated with decreased nerve conduction velocity and increased vibration perception threshold (Bosi et al. Diabetologia (2005) 48: 817–823). This double-blind randomized cross-over versus placebo study demonstrated that after FREMS application there were a reduction in VAS pain score, an increase in sensory tactile perception, a decrease in foot vibration perception threshold and an increase in motor nerve conduction velocity. Moreover benefits were founded also at the 4-months follow-up. Interesting data were obtained in treatment diabetic peripheral vascular disease too. 29 ischaemic legs, with claudication and/or low TCPO2 values, were studied with transcutaneous oximetry and standardized treadmill testing before and after FREMS application. Improvement of oxymetric values and pain free walking distance at 1 month and 3 months were founded (Da Ros et al. Diabetologia, EASD abstract, Copenhagen 14-17 September 2006). Finally an encouraging study with FREMS was performed in the treatment of the acute phase of Charcot’s neuro-arthropathy. This pilot double blind randomized placebo controlled study evaluated 10 patients with an acute Charcot’s neuro-arthropathy. Group treated with FREMS showed a significant improvement in circumference of the foot at dorsum and at the ankle, skin temperature and captation of gadolinium at MR imaging (Tedeschi A, DFSG 2008, Castelvecchio Pascoli, Italy). Results are very encouraging given that few effective therapies are available to treat acute Charcot’s neuro-arthropathy.

**Conclusions**: FREMS represent a new tool in treatment of diabetic related foot complications. Clinical studies demonstrate FREMS effects on VEGF release, increase of microvascular flow with increase of TCPO2 values, improvement in pain control and recovery of peripheral nervous system.