Review Article

Raynaud, Digital Ulcers and Calcinosi in Scleroderma

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A B S T R A C T

Raynaud, digital ulcers and calcinosis are frequent manifestations of patients with systemic sclerosis. Digital ulcers are seen in more than half of the patients with scleroderma. Hospitalizations, ischemic complications and impairment of hand function are frequently observed in patients with digital ulcers, especially if treatment is delayed.

Rapid and intensive treatment escalation in patients with scleroderma and refractory Raynaud’s phenomenon is one of the most effective preventive action available in order to avoid the development of digital ulcers and tissue loss.

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I N T R O D U C T I O N

Despite scleroderma being a rare disease, it is common for rheumatologists in daily practice to receive referrals of patients with Raynaud’s phenomenon and underlying systemic sclerosis.1

Raynaud’s phenomenon may precede by more than 10 years the clinical manifestations of the disease. Because these characteristics of scleroderma overlap with other connective tissue diseases, diagnostic delay is a problem. An early referral on the basis of questioning, physical examination, capillaroscopy and laboratory guide are of paramount importance for diagnosis.1–3

The purpose of this update is to analyze the pathogenic mechanisms and the impact on quality of life of patients with Raynaud’s phenomenon, digital ulcers and calcinosis, as well as its possible treatments, with information from the literature, published guidelines and experience from observational studies.

We must not forget the difficulties reported by several authors at the time of incorporating patients with scleroderma in various controlled studies.4,5

Finally, treating physicians, within the scope of their practice, may apply the knowledge in the difficult management of these patients.6–9

P A T H O P H Y S I O L O G Y

Scleroderma is a complex autoimmune disease that potentially affects all organ systems.

The pathophysiology involves several cell lines, such as endothelium, fibroblasts, lymphocytes and their soluble mediators. These cells set the tone for an early vascular phase with an
inflammatory infiltrate and finally fibrosis. The vascular phase begins in the endothelium of small vessels throughout the body, although the primary event that triggers endothelial damage is unknown. Tissue hypoxia is one of the primary events that modify vascular tone.

Nitric oxide, prostacyclin and endothelin regulate the vascular tone our body. Both nitric oxide and prostacyclin are potent endogenous vasodilators that also have antiproliferative action. In contrast, the endothelin system acts as a counterweight for vascular tone, being a potent vasoconstrictor. Endothelin 1 (ET1) has 10 times the angiotensin 11 vasoconstrictor effect.

Endothelial cells are involved in vascular homeostasis by regulating both muscle tone and cell proliferation. Vasoconstriction is caused by an imbalance of the mediators listed above. Cellular inflammation and perivascular infiltrates with complement deposition and release of proinflammatory mediators complete the picture.

Endothelins are small peptides of 21 amino acids with a potent vasoconstrictor effect. The 3 isoforms of endothelins, ET1, ET2 and ET3, are produced by various cells. Among them, endothelial cells and vascular smooth muscle, distributed in all organs, play a dominant role in the pathogenesis of scleroderma. ET2 and ET3 are distributed differently in kidney, intestine, placenta, uterus, myocardium, brain and to a lesser extent in the lung.

From the viewpoint of pathogenesis, ET1’s role explains the different events in the endothelial phase. ET1 is synthesized in endothelial cells and to a lesser extent in vascular smooth muscle cells. It is also synthesized in mesangial cells, liver cells and cells of the central nervous system.

The ET1 prehormone is activated by the endothelin converting enzyme, and its biosynthesis stimulated by mechanisms such as hypoxia, metabolic disorders and various procoagulants disorders. It is increased in clinical situations, such as hypertension, atherosclerosis, heart failure and renal failure.

In addition to its potent vasoconstrictor action, ET1 has proinflammatory action, promoting cell proliferation and fibrosis. The action of endothelin is genetically encoded by the transforming growth factor beta (TGF-beta), which, by binding to its tissue receptor overexpresses proteins called Smad, which are the genes encoding collagen. Different Smad proteins have different roles, either in the overproduction of collagen and in inhibiting the formation of collagen. This loss of balance is seen in patients with progressive systemic sclerosis.

ET1 exerts its action through two receptors: ET1 A and ET1 B, both different and complementary in action.

The ET1 A receptor is located on smooth muscle cells of pulmonary vessels and favors proliferation,11 vasoconstrictor action and activity.

The ET1 B receptor is located on endothelial cells and to a lesser extent in smooth muscle cells. The action on this receptor varies according to its location: in endothelial cells its vasodilatory action is mediated by the release of nitric oxide and prostacyclin, contributing to the purification of ET1 and inhibition of platelet aggregation. But in the smooth muscle cells, action on the B receptor is vasoconstriction with proliferation and fibrosis.

It has been shown that, in general in scleroderma, both diffuse and limited, serum endothelin levels are increased significantly. This excess endothelin vasoconstriction creates an imbalance between initial and subsequent cell proliferation or remodeling.

These events explain the positive correlation between increased levels of pulmonary pressures and elevated levels of endothelin. Thus the higher levels of endothelin, the higher the values of pulmonary systolic pressure. This supports the dramatic improvement in survival of patients with pulmonary arterial hypertension by blocking endothelin receptor.

Once the endothelial phase of the disease is installed, baseline hypoxia activates the overproduction of endothelin. This excess disturbs the balance of endothelin with nitric oxide and prostacyclins, generating a potent vasoconstrictor action that is not countered, establishing a vicious circle in which the unresolved tissue ischemia leads to increased vasoconstriction, release of proinflammatory cytokines and platelet aggregation as well as stimulation of fibroblast activity. The increase of platelet aggregation with endothelial proliferation and secondary thrombosis promotes remodeling.

Nitric oxide and prostaglandins help maintain the vascular tone balance. Nitric oxide generated by the conversion of L-arginine to L-citrulline produces vasodilation, platelet antiaggregation and inhibition of cell proliferation mediated by cGMP. Prostaglandins, through the arachidonic acid pathway mediated by cAMP, produce vasodilatation with antiinflammatory action. These actions are balanced by a family of phosphodiesterases, which by inhibiting cGMP and cAMP counteract nitric oxide-mediated vasodilation and prostacyclins.

Clinical Manifestations

Raynaud’s Phenomenon

Raynaud’s phenomenon is a transient reversible, vasospastic phenomenon, induced by cold or stress. It occurs in fingers, toes and, less frequently, nose, ears and nipples. It may be asymmetric and not affect all fingers.

Typically, changes in skin color undergo 3 phases: initial pallor, cyanosis, and finally erythema as an expression of a compensatory vasodilatation phase. Analyzing the clinical manifestations of progressive systemic sclerosis, both diffuse and limited, Raynaud’s is present in most patients.

The prevalence of Raynaud’s occurs in less than 10% in the general population.

Secondary Raynaud can occur at any age, while the primary form usually refers to patients in their youth.

Digital Ulcers in Scleroderma

A study of 1614 patients with digital ulcers in scleroderma highlights that defining a digital ulcer can be difficult and complex. This is especially important in relation to the inclusion of patients in various research protocols, in some of which digital ulcer are considered as a loss of the dermis equal to or greater than 2 mm of palmar location on the finger pads of an ischemic etiology.17,18

However, despite the different criteria, digital ulcers in patients with scleroderma may be simply defined as a loss of continuity in the epidermis and adjacent layers and of digital location.

By contrast, ulcer healing involves the complete re-epithelialization of the same, irrespective of pain.

Regarding digital ulcers, we must consider certain features: size, borders, bedding, exposure of tissue (bone, tendons) and presence of underlying calcinosis. An active ulcer is considered acute when it affects more than 6 months.

Digital ulcers in scleroderma patients can be seen in the hands and feet. So-called non-digital ulcers have also been described. Non-digital ulcers in patients with scleroderma are located on the shins, ankles, elbows and forefoot. The leg lesions are generally large and should undergo a differential diagnosis with vasculitis.
The mechanism of development of digital ulcers in scleroderma is due to multiple factors which include repeated microtrauma, thinning skin, dry skin and underlying calcinosis. It is estimated that 8%–12% of ulcers have underlying calcinosis. However, prolonged digital ischemia as an expression of unresolved Raynaud’s phenomenon is the most important risk factor.

The clinical outcome of ulcers depends on the factors listed above. Thirty percent of patients with scleroderma and digital ulcers have a loss of soft tissue and bone. In analyzing the complications of patients with ulcers after 7 years of monitoring, digital gangrene was observed in 11%, but if the treatment fails to reverse the ischemia, virtually 100% of patients with digital ulcers suffer from gangrene afterwards.12 Twelve percent of patients with ulcers require hospitalization and surgery.1,8

When analyzing the different databases of patients with scleroderma, 58% develop at least one digital ulcer at some point in the disease. In 32% of cases, ulcers will become chronic and persistent.8,19 Twenty-five percent of patients with scleroderma in the rheumatology clinic have more than two digital8 ulcers. The ulcers are observed both in patients with a diffuse cutaneous variant and in patients with a limited cutaneous variant of scleroderma.

The impact on the quality of life and disability of patients with digital ulcers can objectify scleroderma through the HAQ, visual scale for pain, scale of severity of the ulcer, loss of limb function and the loss of joint function related to the ulcer.8

Disability generating digital ulcers may be transient or permanent.

**Calcinosis**

Patients with limited scleroderma most often develop calcinosis. These calcium deposits are located in soft tissues, without causing direct joint involvement, and may be small or large and usually complicated by skin ulceration and superimposed infection.

The main pathophysiological mechanism for the development of calcinosis in scleroderma is tissue hypoxia.20 This decrease in perfusion is accompanied by inflammatory cell activity and macrophage activation as well as an imbalance between various mediators that cause increased calcium influx to cells.20

Patients with extensive calcinosis exhibit significant impairment of functional capacity due to flexion contractures of the adjacent joints. When calcinosis breaks the skin, ulcerative lesions develop with the possibility of bacterial superinfection.

According to their origin, calcification of soft tissues can be classified into different variants: metastatic, dystrophic or idiopathic calciphylaxis. Dystrophic interests us in connection with scleroderma, because it originates in tissues affected by hypoxia caused by decreased perfusion and normal mineral metabolism.

**Diagnostic Aspects**

In the diagnosis of patients with Raynaud’s phenomenon nailfold capillaroscopy is crucial, to separate those patients with primary Raynaud’s phenomenon from patients with underlying connective tissue disease.3

The first diagnostic approach is achieved through interrogation: unlike patients with primary Raynaud, patients with secondary Raynaud’s associated with connective tissue diseases have more severe attacks and are at risk for ischemic lesions with permanent tissue damage.2,6

Nail bed capillaroscopy can be performed with 3 different instruments, depending on the resources available and the physician’s prior training. It may be performed with a stereo binocular microscope which magnifies up to 40 times, with a videocapillaroscope, or a handheld digital microscope connected to a computer.3

Upon completion of capillaroscopy, office temperature should be 22–25 °C to avoid cold-induced Raynaud.

Eight fingers should be examined, the second through the fifth fingers of each hand, and the most representative image or pattern is reported. Normal is defined as the presence of 9–11 capillaries aligned in a linear field of 1 mm, in the middle of the nailbed.3

The following changes must be described: hemorrhages, elongated megacapillaries, decreased number of capillaries, ramified capillaries and capillary disorganization of the nail vascular tree.

In turn, in accordance with prevailing disturbances, 3 types of capillaroscopic patterns exist: early, active and late. In connection with the change from one pattern to another, it has been suggested that capillaroscopy be repeated every 6 months.21

Nailfold capillaroscopy will establish a qualitative pattern, a quantitative score and a predictive value index of the risk for ulcer development.22,23

A validation has recently been published for the capillaroscopic index of risk for development of digital ulcers in scleroderma patients. This index allows, with high sensitivity, high specificity and high predictive value, to define those patients at high risk for developing digital ulcers within 3 months of the initial21 capillaroscopy.

Regardless of the possibility of the capillaroscopic risk index offering a high predictive value for developing digital ulcers with the simple observation of less than 4 capillaries per millimeter on the linear nail bed capillaroscopy, a history of ulcers is clinically more predictive and important for the development of new digital ulcers.22,23

In patients without an established diagnosis of scleroderma, Raynaud’s phenomenon, sclerodactyly and the presence of antinuclear antibodies are the so-called “red flags.”

Those with those 3 red flags and a capillaroscopy suggestive of the disease and either the presence of autoantibodies, anticentromere or anti Scl70, constitute the subgroup of patients with so called early scleroderma (VEDOSS, very early diagnosis of systemic sclerosis).24

The ability to diagnose the disease early will allow adequate and complete tracking of all other manifestations of scleroderma.

**Therapeutic Aspects**

While both Raynaud, digital ulcers and calcinosis are clinical manifestations, there is no specific treatment is unique to scleroderma-like disease in itself. Treatments are aimed at the involvement of each organ or system in particular.25

When we talk about the therapeutic aspects, we must remember that uncontrolled or refractory Raynaud, especially that associated with connective tissue diseases, can lead to permanent tissue damage. On the other hand, in patients with digital ulcers or tissue damage already established, the goal is not only healing, but also preventing the development of new ulcers digitales.5,8,9

The underlying calcinosis unresolved delay or prevent healing of digital ulcers.

When defining each patient treatment should be instituted by a hand considering the indications according to technical specifications for the different drugs and, secondly, the proposed
treatment based on the recommendations of various working groups, scientific societies, the published studies, some of them open, uncontrolled but significant number of patients included.

By indicating the drug with higher levels of evidence, we must remember the difficulties reported in recruiting patients for clinical trials in scleroderma randomized controlled both by design errors as well due to the low prevalence of disease. 1.5

**Treatment of Raynaud’s Phenomenon**

The therapeutic approach to Raynaud’s phenomenon depends, first, on whether it is primary or secondary. Patients with secondary Raynaud’s have episodes that are more severe, frequent and prolonged. Under these conditions the presence of tissue ischemia defines the therapeutic behavior. 2.6.7

The drugs indicated are those designed to change reversible vasoconstriction. Patients with primary Raynaud’s phenomenon have attacks of shorter duration and intensity and require, first, the correction of various triggering factors.

Patients with Raynaud’s phenomenon associated with scleroderma require drug treatment, and aggressive steps in relation to the lack of response. 6 Failure to respond will be defined by the persistence of the different phases of Raynaud despite appropriate treatment.

In the treatment of Raynaud, calcium channel blockers are the first step in.6,25,26 Given the lack of response, drugs such as sildenafil may be added. Both iloprost and bosentan are reserved for refractory cases and critical tissue ischemia 6 and damage.

Improvement has been measured in Raynaud’s with thermography of the hands in patients treated with bosentan.27

In patients with scleroderma and non-digital ulcers, perilesional cyanosis as an expression of Raynaud and unresolved tissue damage can be considered as a predictor of good response in patients treated with bosentan.28

Other authors have also highlighted the importance of treatment of severe refractory Raynaud with bosentan.29–32

Specifically, in terms of severe or serious Raynaud, with possible injury or development of ischemic tissue, various publications include algorithms and diagrams that provide a range of options ranging from general care to different drugs, and eventually hospitalization to initiate an infusion of prostacyclin and eventually perform a sympathectomy as an emergency measure. 2.6,8,26

When analyzing the schemes proposed for the treatment of severe Raynaud’s, there are similarities with the various reports of reported treatment for the prevention and healing of digital scleroderma ulcers.8,29–37

In the presence of critical ischemia, or the lack of response, or causal, the involvement of major vessels, vasculitis or associated coagulopathy 9 should be considered also as a trigger.

**Treatment of Digital Ulcers in Scleroderma**

Both prevention and treatment of digital ulcers in scleroderma patients is important to note as a parameter of response to treatment, both in the evolution of Raynaud as in pain of ischemic origin. If Raynaud and hence tissue ischemia is prolonged, or underlying calcinosis is not resolved, ulcers are difficult to cure and, once installed, tend to become chronic.

The persistence of pain may be an expression not only ischemia but also superimposed infection.

The drugs may be scaled as determined by each physician and in the order that the situation warrants, in accordance to the response.6–9,25,26 Even for severe refractory cases the combination of them may be considered, but there is insufficient experience to endorse this.

Regarding prevention and treatment of digital ulcers in scleroderma patients with active ulcers one must consider:

1. General measures.
2. Pharmacological measures.
3. Surgical options.

**General Measures**

- Define hospitalization criteria.
- Soothe the pain, considering the need for the use of opiates.
- Warm the environment.
- Sedation: avoid stress, as this increases sympathetic tone, resulting in greater contraction.
- Check Raynaud periodically.
- Avoid contraceptives due to their prothrombotic action.
- Avoid coffee and tobacco.
- Avoid the use of vasoconstrictive drugs such as decongestants, amphetamines, ergotamine, etc.
- Avoid cold by wearing gloves.
- Caring for the skin with the use of moisturizers on normal skin and handwashing with antiseptic soap.
- Avoid repeated microtrauma of the hands.
- Consider the possibility of bacterial infection and antibiotic treatment.
- Consider wide surgical removal of infected tissue, necrotic tissue or calcinosis in each particular case.
- Facilitate the healing of an ulcer with local treatment with vitamin E ointment.

**Pharmacological Measures**

**Antiplatelet Drugs**

- Aspirin at an antiplatelet dose.
- Low molecular weight heparin (LMWH).

**Vasodilators**

- Cilostazol.
- Inhibitors of type 5 phosphodiesterase.
- Calcium channel blockers.
- Bosentan.
- Prostacyclin analogues.

**Other Drugs**

- Serotonin receptor antagonists and reuptake inhibitors.
- N-acetylcysteine.
- Statins.
- Botulinum toxin A.
- Topical vitamin E gel.

**Inpatient and Secondary Prevention of Thrombosis**

In the case of single or multiple digital ulcers we must consider the need for an outpatient clinic that facilitates medical management and quickly establish interdisciplinary and general measures.

Laboratory assessments should include the search for a probable associated coagulopathy and tracking of including lupus anticoagulant, anticardiolipin and anti-beta2-glycoprotein antibodies.
Eventually and in a preventive manner, consider LMWH to prevent secondary thrombosis in patients who are suffering from vasoconstriction and endothelial damage with greater tendency to platelet aggregation.3,38

### Bosentan

Several studies have reported the efficacy of bosentan for the prevention and treatment of digital ulcers in patients with active scleroderma.17,18,33–37,39

According to technical data, bosentan is indicated for the treatment of pulmonary arterial hypertension (group I functional class II to IV) and for reducing the number of new digital ulcers in patients with systemic sclerosis (scleroderma) with ongoing disease.

Bosentan is a dual antagonist of endothelin receptors. Blockade of endothelin receptors can be done in two ways: with greater selectivity for the A receptor, e.g. ambrisentan and sixtasentan (recalled due to liver toxicity), or in a dual form, blocking both the A and B receptors, which is the mechanism of action of bosentan.

Clinical benefits of selective blockade vs dual blockade of endothelin are unknown. To date, bosentan is the only endothelin receptor antagonist approved for digital ulcers. Ambrisentan is only approved for pulmonary arterial hypertension.

The efficacy of bosentan in the prevention of new digital ulcers has led to its approval was demonstrated in 2 randomized, double-blind, placebo-controlled multicentric trials.17,18 One study included patients with scleroderma who had a history of digital ulcers during the previous year but did not present active ulcers on inclusion, while the other study included subjects with active digital ulcer disease. Both studies evaluated prevention and healing of digital ulcers, differentiating ulcer healing on the one hand and all ulcers (old and new) on the other.17,18 These 2 studies show that bosentan achieved prevention in the development of new digital ulcers ranging from 30% (1.9 vs 2.7 new ulcers) to 48% (1.4 vs 2.7 new ulcers) of patients, according to whether patients had or did not have active ulcers at study entry, respectively. In the data related to healing in the group of patients with active ulcers at inclusion, ulcers healed in 50% of patients in both groups (bosentan group vs placebo group), while all digital ulcers (old and new combined) were cured in 36.8% of patients in the bosentan group and 39.3% of patients receiving placebo.18 These cure rates of both the cardinal ulcer, the old and new ulcers were similar for both groups, bosentan and placebo at 24 weeks.18 In this regard, it is important to analyze the demographics of the population included, because patients receiving various drugs with vasodilator action were found in both groups.17,18 The reduction in the number of new digital ulcers (prevention) in patients treated with bosentan was more evident in the group of patients with 4 or more digital ulcers upon admission to the study.18

A retrospective multicenter open-label study done in Spain and published in 2011 analyzed the results obtained with bosentan in 67 patients with scleroderma ulcers, followed at 12 and 24 months. The authors showed significant improvement of both active ulcers and in prevention of ulcers. The median time of treatment with bosentan was 13 months with a sustained efficacy follow-up. At the 12-month assessment (n=22), 81% had improved and 18.2% had stabilized ulcers. In terms of prevention, at 12 months, 68% of patients developed new ulcers.39

Anecdotally, we have reported an improvement in the skin score in patients treated with bosentan.40,41 This could hypothetically contribute to the improvement of digital ulcers by reducing the induration of patients with scleroderma.

### Calcium Channel Blockers

Nifedipine and amlodipine are the most common: they reduce the intensity and frequency of Raynaud attacks. Calcium channel blockers are of limited use in general, due to poor efficacy and a high frequency of side effects: headache and lower limb edema. Doses should be scaled relative to the response and patient tolerance. Long-acting formulations are generally better tolerated.42,43 They should be used with caution due to possible negative inotropic effects.

In some reports, losartan had similar results or better than nifedipine.44

### Nitroglycerin Patches

Transdermal nitroglycerin patches have been used in a small number of patients with good efficacy but with systemic effects such as headaches and hypotension.45,46

### Inhibitors of Type 5 Phosphodiesterase

Sildenafil and tadalafil are phosphodiesterase inhibitors that achieve vasodilation by increasing nitric oxide. These drugs have effects on both micro and macrovascular circulation.

Sildenafil reduces Raynaud and, according to some studies, may be effective in promoting healing of digital ulcers. However, the doses required cause headache that limits their use. Efficacy has been evaluated both in clinical and imaging by determining Doppler digital flow or digital thermography in open studies or case reports.47–50

### Iloprost and Prostacyclin Analogues

Iloprost and treprostinil have been used in trials with small numbers of patients and have been reported as effective for treating refractory Raynaud associated with scleroderma and the healing of digital ulcers.51,52 They require strict patient monitoring in hospital. A pump failure or catheter compression that suddenly stops the drip may produce death by drug rebound. Serious catheter related infections have also been reported.

Another prostaglandin analog, alprostadil, administered intravenously 5 days in a row, has also been used in patients with refractory Raynaud.53

### Cilostazol

Cilostazol is a selective inhibitor of phosphodiesterase III with antiplatelet and vasodilatory actions that can help improve blood flow, especially in patients with primary Raynaud and that associated with connective tissue disease.54

### Other Pharmacological Treatment Options

#### Serotonin Receptor Antagonists and Reuptake Inhibitors

With respect to serotonin receptor antagonists and reuptake inhibitors, the information is contradictory. There has been improvement in Raynaud patients taking fluoxetine, sertraline and escitalopram, probably due to depletion of platelet serotonin.55–57

But, there are reports of worsening Raynaud’s with these drugs, including digital58,59 necrosis.
N-Acetylcysteine

N-acetylcysteine intravenously has shown benefit in a small open study in patients with Raynaud’s, scleroderma and digitales ulcers.

Statins

In a group of patients with Raynaud’s and scleroderma, 40 mg of atorvastatin/day reduced the number of new ulcers compared with placebo (vasodilators), even changing endothelial dysfunction markers.

Botulinum Toxin

Occasionally, the interdigital injection of botulinum toxin, both in patients with primary and secondary Raynaud’s may be beneficial.

Vitamin E Topical Gel

Regarding local treatment, topical vitamin E gel may contribute to the improvement and healing of digital ulcers.

Surgical Options

Chemical or surgical, cervical, thoracic or digital ultraselective sympathectomy may be considered as an emergency measure to surgical resolution may be considered in cases of extensive deposits of calcium that cause flexion contractures or impaired joint function but remembering that these injuries tend to become infected and are difficult to heal. For smaller localized lesions, CO2 laser and extracorporeal shock wave techniques can be useful.

The case of a patient with scleroderma and extensive calcinosis complicated with skin infections who responded well to rituximab has recently been reported.

Conclusions

Raynaud’s phenomenon, calcinosis and digital ulcers in scleroderma patients produce varying degrees of disability. Many patients present with ongoing ulcers in the clinic.

It is important to exhaust all therapeutic instances, both those aimed at preventing the occurrence of new ulcers as those designed to achieve rapid healing before the permanent loss of tissue.

To achieve the reversal of Raynaud’s is the first step to avoid tissue ischemia.

Calcinosis should be resolved in order to facilitate the healing of ulcerated lesions.

Ethical Responsibilities

Protection of Human and Animal Subjects. The authors declare that no experiments were performed on humans or animals for this investigation.

Confidentiality of Data. The authors declare that no patient data appear in this article.

Right to Privacy and Informed Consent. The authors must have obtained the informed consent of the patients and/or subjects mentioned in the article. The author for correspondence must be in possession of this document.

Conflict of Interest

The author has no disclosures to make.

References


