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Modern Approaches to Raynaud's Phenomenon: Pathophysiology, Treatment, and Emerging Therapies - Review of the literature

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Abstract

Raynaud's phenomenon (RP) is a multifactorial vasospastic disorder characterized by episodic digital ischemia, commonly triggered by cold exposure or emotional stress. RP may present as primary (idiopathic) or secondary, the latter often associated with systemic sclerosis or other connective tissue diseases and carrying a higher risk of complications such as digital ulcers and tissue loss. This narrative review aims to synthesize current evidence on the pathophysiology, clinical manifestations, and management strategies for RP, including non-pharmacologic interventions, pharmacologic therapies, surgical approaches, and adjunctive nutraceuticals.

Material and Methods: We reviewed recent open-access literature from the past few years, including randomized controlled trials, meta-analyses, and systematic reviews, alongside mechanistic studies and guideline recommendations, to provide a comprehensive overview of current therapeutic approaches.

Results

Non-pharmacologic measures, including trigger avoidance, temperature management, smoking cessation, and patient education, remain foundational, particularly for primary RP. Calcium channel blockers are first-line pharmacologic agents, reducing attack frequency, duration, and severity. Second-line therapies include phosphodiesterase-5 inhibitors and prostanoids, primarily intravenous iloprost, for refractory or ischemic cases. Endothelin receptor antagonists prevent digital ulcer recurrence in secondary RP. Botulinum toxin injections and surgical interventions, such as digital sympathectomy or angioplasty, may benefit selected patients with severe disease. Adjunctive dietary supplements, including omega-3 fatty acids, Ginkgo biloba and antioxidant vitamins, show biological plausibility but lack high-quality clinical evidence. Across all treatment modalities, high-quality randomized controlled trials remain limited, and standardized outcome measures are inconsistently applied.

Conclusion

Management of RP requires an individualized, stepwise approach combining lifestyle modifications, pharmacologic therapy, and, when indicated, invasive or adjunctive interventions. Significant gaps remain in high-quality evidence, highlighting the need for multicenter trials, standardized outcome reporting, and further mechanistic studies to optimize patient care and long-term outcomes.

Key words: Raynaud's Phenomenon, Primary Raynaud, Secondary Raynaud, Vasospasm, Digital Ulcers

Introduction

Raynaud's Phenomenon (RP) is a clinically significant vasospastic disorder characterized by episodic, reversible constriction of peripheral blood vessels, most commonly affecting the digits in response to cold exposure or emotional stress, and manifesting as distinctive color changes from pallor to cyanosis and erythema. RP occurs in both primary (idiopathic) and secondary forms, the latter often associated with underlying systemic diseases such as connective tissue disorders, and in some cases can lead to considerable morbidity including digital ulceration and tissue loss. (1)

The overall prevalence of RP in the general population is estimated at approximately 3-5%, with variability driven by differences in diagnostic criteria, geographic region, sex, and environmental exposures. (1,2) Primary RP tends to be more common in younger individuals and typically follows a benign clinical course, whereas secondary RP may present later in life with asymmetrical symptoms and a higher risk of complications due to its association with microvascular structural abnormalities. (3)

The pathophysiology of RP is complex and multifactorial, involving an intricate interplay between neural, vascular, and humoral mechanisms that disrupt the equilibrium between vasoconstrictive and vasodilatory forces in peripheral microcirculation. Functional vascular dysregulation, endothelial dysfunction, and augmented sympathetic activity contribute to the exaggerated vasospastic response, but precise mechanistic pathways remain incompletely understood. (1)

Despite advances in understanding RP, no universally accepted cure exists, and management typically aims to reduce the frequency and severity of vasospastic episodes, improve patient quality of life, and prevent progression to tissue injury. First-line strategies emphasize avoidance of triggers and lifestyle modification - pharmacological interventions, including calcium channel blockers and other vasodilators, are used in more symptomatic cases. Increasing attention is also being given to dietary supplements, non-drug modalities, and

lifestyle or exercise interventions that may modulate symptom expression and vascular function. (1)

This narrative review synthesizes current evidence on pharmacologic treatment, dietary supplements, and the role of lifestyle and exercise in symptom modulation for RP, highlighting clinical considerations, emerging therapeutic insights, and areas requiring further research.

Pathophysiology of Raynaud's Phenomenon

Raynaud's Phenomenon (RP) is a multifactorial disorder arising from the interplay of genetic, vascular, neural, intravascular, and humoral mechanisms (3,4,5). Clinically, RP is classified as primary (PRP) or secondary, the latter often associated with systemic sclerosis (SSc) or other connective tissue diseases, and generally exhibiting greater severity and higher risk of ischemic complications (3,6)

Genetic factors influence susceptibility to RP. Familial clustering and twin studies suggest a heritable component, with up to 50% of primary RP patients reporting affected first-degree relatives (4). Variants in genes regulating vascular function, such as NOS1, may predispose the vasculature to hyperreactive responses to environmental triggers, particularly cold (4,7).

Vascular hyperreactivity is central to RP pathophysiology. In primary RP, functional abnormalities predominate: thermoregulatory arteriovenous anastomoses (AVAs) demonstrate exaggerated vasoconstriction in response to cold, while nutritive capillaries remain intact, preventing tissue ischemia (3). In secondary RP, structural defects coexist with functional dysregulation. Endothelial dysfunction manifests as increased production of vasoconstrictors, including endothelin-1 and angiotensin II, alongside impaired vasodilation due to reduced nitric oxide and prostacyclin activity (8,9). Capillary loss and occlusion exacerbate ischemia, particularly in glabrous, hairless skin, explaining the digital predilection (3,10). Vascular patency is influenced by the balance between arterial wall tension and intravascular distending pressure, with secondary RP often showing lower brachial and digital arterial pressures due to occlusive disease or prior vascular injury (5).

Neural mechanisms further amplify vasospastic responses. Primary RP is characterized by local dysregulation of thermoregulatory vascular function, while secondary RP may involve central autonomic contributions (3,4). Cold exposure triggers α_2C adrenergic receptor translocation through RhoA/ROCK activation, increasing contractile sensitivity. Enhanced sympathetic

activity promotes neurotransmitter-mediated vasoconstriction, and peripheral nerve compression, such as in thoracic outlet syndrome, may worsen episodes (3). Dysregulation of vasoactive peptides, including calcitonin gene-related peptide, also modulates vascular tone (4).

Intravascular and humoral factors contribute to RP pathogenesis. Altered blood rheology, platelet and leukocyte activation, and reduced erythrocyte deformability impair microvascular flow (11). Fibrinolysis is often impaired in secondary RP but remains normal in primary RP (3). Hematological disorders increasing plasma viscosity, such as polycythemia vera, Waldenström macroglobulinemia, cryoglobulinemia, and cold agglutinin disease, may reduce digital perfusion (4,5). Dysregulated vasoactive mediators-including serotonin, thromboxane A_2, and endothelin-1-further enhance vasospasm, with ET-1 antagonists reducing digital ulceration in scleroderma-associated RP (12).

In summary, RP results from a synergistic interaction of vascular hyperreactivity, neural dysregulation, endothelial dysfunction, intravascular abnormalities, and humoral mediators. Primary RP is dominated by functional disturbances, causing episodic ischemia without structural injury, whereas secondary RP combines these functional alterations with structural vascular damage and rheological impairment, leading to more frequent and severe ischemic episodes. Together, these mechanisms explain the episodic nature, cold sensitivity, and digital predilection characteristic of RP (3,5).

Primary vs Secondary RP

Primary Raynaud's Phenomenon typically affects young individuals, most often women, with symptom onset between 15 and 30 years of age and a strong familial predisposition, as up to 30-50% of first-degree relatives may be affected (13). Microcirculatory changes in primary RP are functional rather than structural, with preserved vascular architecture, frequent thumb sparing, and reversible ischemia as a defining feature (3). Pain or paresthesia is uncommon, trophic changes and digital ulcers are absent, peripheral pulses are symmetrically normal, and laboratory findings usually show negative or low-titer antinuclear antibodies (ANA) with a normal erythrocyte sedimentation rate (ESR) (4). Nail fold capillaroscopy typically appears normal (13).

In contrast, secondary Raynaud's Phenomenon generally presents later in life, often after the age of 40 years, with sex distribution varying according to the underlying condition. It is characterized by combined structural and functional microvascular impairment, more frequent and sometimes severe pain or paresthesia, and a higher risk of ischemic tissue injury, including

digital ulcers and trophic changes such as sclerodactyly or telangiectasia (14). Ischemia may be progressive and irreversible, peripheral pulses can be asymmetric or reduced depending on etiology, and laboratory evaluation often reveals positive ANA and elevated ESR. Nail fold capillaroscopy commonly demonstrates abnormal capillary morphology, reflecting underlying microvascular damage (15). Figure 1 illustrates the secondary causes of Raynaud's phenomenon.

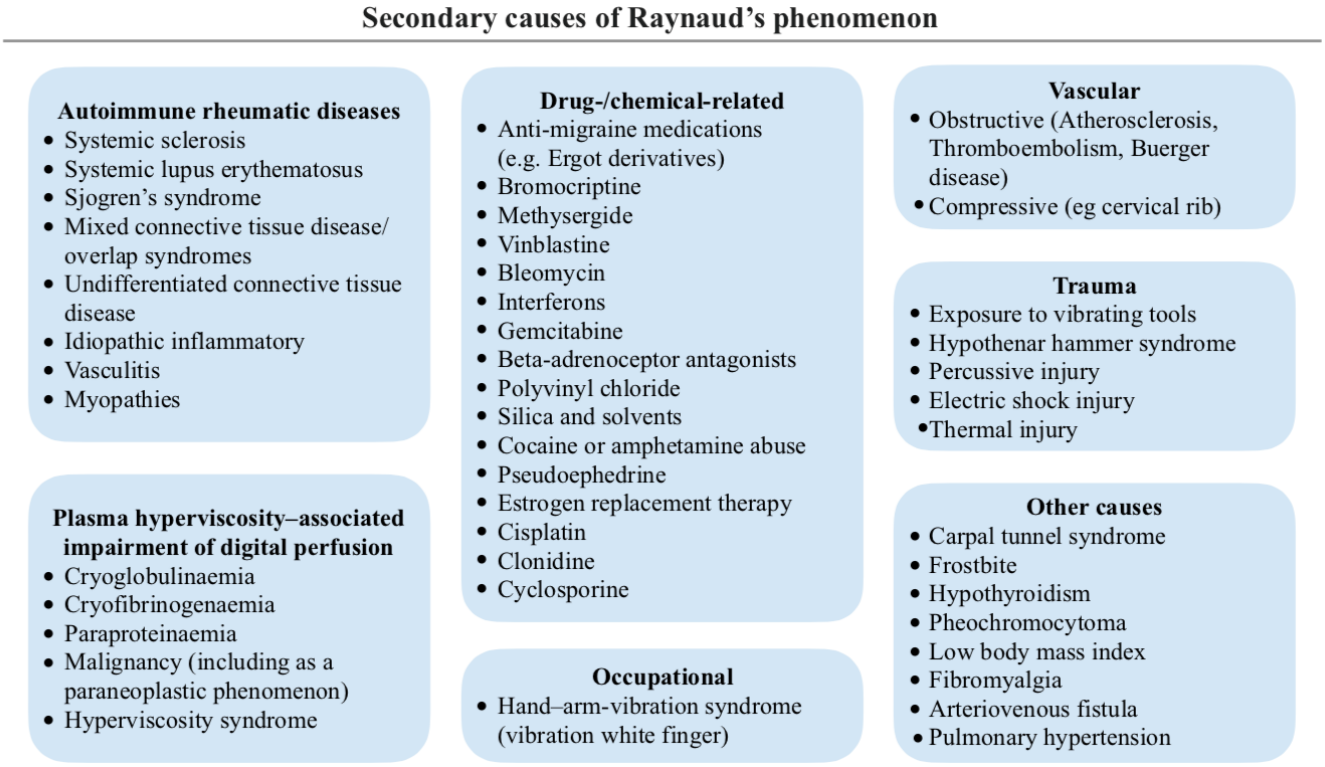

Figure 1. Secondary causes of Raynaud's phenomenon (3,4).

Clinical Manifestation

Raynaud's Phenomenon (RP) is a clinical manifestation of episodic vasospastic events characterized by reversible skin color changes, frequently accompanied by neurosensory symptoms such as pain, numbness, tingling, and discomfort (16). Typical RP attacks are precipitated by cold exposure and/or emotional stress and most commonly affect the hands and feet, although other vascular regions - including the lips, nose, ears, and nipples - may also be involved (4).

The classical presentation consists of a triphasic sequence of color changes: pallor resulting from vasoconstriction, cyanosis due to sequestration of deoxygenated blood, and erythema associated with reperfusion and reactive hyperemia (4,16).

Importantly, the presence of all three phases is not required for diagnosis, and most classification systems support the identification of RP based on at least two color changes (4,16). Cyanosis occurring without prior pallor is more commonly observed in systemic sclerosis - associated RP, whereas reactive hyperemia is less prominent compared with primary RP (4).

Therapeutic Strategies in Raynaud's Phenomenon

The management of Raynaud's phenomenon (RP) aims to reduce the frequency and severity of vasospastic attacks and to prevent disease-related complications. Non-pharmacological interventions represent the foundation of treatment and are recommended for all patients, particularly those with primary Raynaud's phenomenon, in whom such measures may be sufficient to control symptoms (16,14).

Pharmacological therapy is considered in patients with persistent or severe symptoms - however, evidence supporting its use is limited by a lack of large randomized controlled trials (RCTs). The episodic nature of RP poses an additional therapeutic challenge, as effective prevention of attacks often requires long-term medication use, which may be associated with adverse effects (16,17).

In refractory cases, especially in secondary RP, interventional approaches such as botulinum toxin injections and sympathectomy may be employed (16,18). Moreover, the management of secondary RP includes treatment of complications such as digital ulcers, ischemic necrosis, and secondary infections, which may require antibiotic therapy, specialized wound care, or surgical intervention (14,18).

Non-pharmacological management

Non-pharmacological interventions constitute the foundation of management in all patients with Raynaud's phenomenon (RP) and are recommended regardless of disease severity or etiology. These measures aim to reduce the frequency of vasospastic episodes, limit symptom severity, and prevent ischemic complications, particularly in patients with primary RP, in whom lifestyle-based strategies may be sufficient for symptom control (1,4,16).

Patient education plays a central role in non-pharmacological management. Individuals with RP should receive clear, high-quality information regarding the nature of the disease, potential triggers, and practical strategies for symptom prevention. Referral to patient-led organizations and access to educational materials, including online resources, may provide additional support and improve self-management (4,16).

Cold avoidance remains the most important preventive strategy. Patients should be advised to maintain adequate peripheral and core body temperature through the use of layered clothing, hats, insulated footwear, gloves or mittens, and portable heat packs. Protective measures such as using holders when handling cold objects and avoiding tight-fitting shoes or socks are also recommended. When rewarming is required, warm water may be used cautiously - however, exposure to hot water should be avoided due to the risk of thermal injury in areas with impaired sensation or perfusion (16,19).

Smoking cessation should be strongly encouraged in all patients with RP, as nicotine is a potent vasoconstrictor and has been shown to reduce cutaneous blood flow, thereby exacerbating vasospastic attacks. Patients should also be advised to avoid passive smoke exposure (5,16,19).

Identification and avoidance of additional triggers is an important component of management. Emotional stress and anxiety are well-recognized precipitants of RP attacks, and stress-reduction strategies such as regular physical activity, relaxation techniques, yoga, or meditation may reduce attack frequency. Occupational and environmental factors, including exposure to vibrating tools or repetitive microtrauma, should be minimized where possible (3,19).

Patients should also be counseled regarding medications and substances that may worsen vasoconstriction. These include nasal decongestants containing sympathomimetics (e.g., pseudoephedrine), amphetamines, ergot derivatives, and excessive caffeine intake in susceptible individuals. Regular review of prescribed and over-the-counter medications is therefore recommended (3).

Skin care represents an additional preventive strategy, particularly in patients at risk of digital ischemia. Regular use of emollients can help prevent skin dryness and fissuring, while routine inspection of fingers and toes may allow early detection of ulcers or other ischemic lesions (19).

Finally, many patients explore complementary or alternative therapies, such as antioxidant supplementation. Current evidence supporting their efficacy in RP remains limited, and clinicians should actively inquire about their use, particularly due to the potential for interactions with pharmacological treatments (16).

Calcium channel blockers

Calcium channel blockers (CCBs) are widely regarded as the first-line pharmacological agents in the management of RP. Their therapeutic effect is mediated by inhibition of calcium influx through voltage-sensitive L-type calcium channels in vascular smooth muscle cells, leading to smooth muscle relaxation and improved peripheral blood flow (3,21). Among the available CCB classes, dihydropyridine CCBs are preferred because of their predominant action on peripheral vasculature and relatively lower cardiac effects compared with non-dihydropyridine agents (21,22).

The most commonly used dihydropyridine CCBs in clinical practice are nifedipine and amlodipine. Nifedipine has been the most extensively studied agent in clinical trials, while amlodipine is frequently prescribed due to its favorable dosing schedule and tolerability profile (3,20). Extended-release or long-acting formulations are generally recommended, as they are associated with more stable plasma concentrations and reduced sympathetic activation compared with immediate-release preparations (3,21). Short-acting formulations may be reserved for urgent situations or severe disease, although their routine use is discouraged (20).

Treatment with CCBs should be initiated at the lowest effective dose and titrated gradually based on clinical response and tolerability. Typical dosing regimens include amlodipine starting at 5 mg once daily, with escalation to 10 mg daily if needed, and modified-release nifedipine starting at 10-30 mg daily, with gradual increases up to 40 mg twice daily or higher in selected cases (16,21). Blood pressure monitoring is essential, particularly in patients with baseline hypotension (20).

Evidence supporting the efficacy of CCBs in RP has been derived largely from randomized controlled trials and meta-analyses, although study quality and methodology have varied. Early meta-analyses demonstrated modest reductions in attack frequency and severity, with limited effects on attack duration (3,21). Larger and more recent analyses, including reviews of up to 38 randomized controlled trials, have shown that CCB therapy is associated with reductions in

the frequency, duration, and severity of RP attacks, with greater benefit observed in patients with primary RP compared to secondary RP (5,22). However, the magnitude of benefit has been described as moderate, and heterogeneity among studies remains a limitation (5).

The role of CCBs in the prevention or healing of digital ulcers is less well established. Available evidence suggests that while CCBs may improve vasospastic symptoms, their effectiveness in promoting ulcer healing or preventing ischemic complications is limited, particularly in secondary RP (3,21).

Adverse effects associated with dihydropyridine CCBs are dose dependent and commonly include peripheral edema, headache, dizziness, flushing, palpitations, and reflex tachycardia. These side effects contribute to treatment discontinuation in a subset of patients, as demonstrated by higher withdrawal rates in CCB-treated groups in clinical trials (5,20).

Contraindications to CCB therapy include significant hypotension, severe peripheral edema, unstable angina, recent myocardial infarction, severe aortic stenosis, hypertrophic cardiomyopathy, and advanced pulmonary hypertension. Use during pregnancy is generally avoided unless severe digital ischemia is present (20).

Despite these limitations, calcium channel blockers remain the most extensively studied and widely used pharmacological option for RP. At present, no other oral vasodilator class has demonstrated superior efficacy in primary RP, reinforcing the role of dihydropyridine CCBs as the cornerstone of pharmacological management (1).

Phosphodiesterase-5 Inhibitors

Phosphodiesterase-5 (PDE-5) inhibitors are commonly used as second-line therapy in patients with Raynaud’s phenomenon (RP) who remain symptomatic despite calcium channel blocker treatment, particularly in secondary RP associated with systemic sclerosis. By inhibiting cGMP degradation, these agents enhance nitric oxide - mediated vasodilation and improve peripheral perfusion (16,23).

Evidence from randomized trials suggests modest but clinically relevant benefits. A review of nine RCTs (411 participants) demonstrated that PDE-5 inhibitors reduced attack frequency by approximately three episodes per week and shortened daily attack duration by several minutes

compared with placebo, although the certainty of evidence was low. Improvements in severity and global assessments were reported, while reductions in pain were minimal (24). A separate meta-analysis similarly confirmed decreases in attack frequency and duration (16).

Sildenafil is most frequently prescribed, typically initiated at 20 mg daily and titrated up to 20 mg three times daily according to response and tolerability. Tadalafil, owing to its longer half-life and once-daily dosing, may be used as an alternative or add-on therapy. Concomitant use with nitrates should be avoided due to the risk of hypotension (16,23,25).

Adverse effects are generally mild and include headache, flushing, and hypotension. Other phosphodiesterase inhibitors have not consistently demonstrated clinical benefit. PDE-5 inhibitors may also support digital ulcer healing when combined with other vasodilators, although further evidence is needed (24-26).

Overall, PDE-5 inhibitors represent a reasonable second-line option, particularly in secondary or more severe RP, despite moderate efficacy and limited high-quality data.

Prostaglandin Analogs

Prostaglandin analogs (prostanoids) are reserved for patients with severe or refractory Raynaud's phenomenon (RP), particularly those with critical digital ischemia or active ulcers. In addition to potent vasodilation, these agents inhibit platelet aggregation and improve microvascular perfusion (3,27).

Intravenous iloprost, a prostacyclin analog, is the best-studied therapy in this group. Short courses of IV infusion have been shown to reduce attack frequency and severity and to promote digital ulcer healing, especially in systemic sclerosis-associated RP. Clinical benefits are often temporary, and repeated treatment cycles may be necessary (16,27). Adverse effects are mainly infusion-related and include headache, flushing, nausea, and hypotension (3,16).

Oral and inhaled prostanoids have demonstrated inconsistent or limited efficacy compared with intravenous therapy, and their role remains uncertain (1,3).

Overall, IV prostanoid therapy represents an important option for patients with ischemic complications when standard vasodilator treatments are insufficient.

Endothelin Receptor Antagonists

Endothelin receptor antagonists (ERAs) represent a targeted therapeutic option for patients with severe secondary Raynaud's phenomenon, particularly in the context of systemic sclerosis-associated vasculopathy complicated by recurrent digital ulcers. Endothelin-1, a potent vasoconstrictor and profibrotic mediator, contributes to endothelial dysfunction and sustained digital ischemia, thus receptor blockade may mitigate these pathogenic mechanisms (28).

Bosentan, a dual endothelin A/B receptor antagonist, is the most extensively studied agent in this class. Randomized controlled trials (RAPIDS-1 and RAPIDS-2) demonstrated that bosentan significantly reduces the development of new digital ulcers, although it has limited efficacy in promoting healing of established lesions or consistently improving the frequency and severity of Raynaud's attacks (29,30). Consequently, its clinical role is primarily preventive in patients with recurrent or refractory ulceration despite standard vasodilator therapy. Treatment requires monitoring because adverse effects, including peripheral edema and elevated liver transaminases, are relatively common (29).

Other ERAs, such as macitentan, have not shown comparable benefit in controlled studies, and therefore their routine use in Raynaud's phenomenon is not currently supported (31).

Other Pharmacologic Therapies in Raynaud's Phenomenon

In patients who do not respond adequately to first-line vasodilators (e.g., calcium channel blockers) and second-line agents such as phosphodiesterase-5 inhibitors or prostanoids, a number of additional pharmacologic therapies have been evaluated. However, the overall evidence for many of these agents is limited in quantity and quality, with inconsistent efficacy across studies (26,32).

Adrenergic alpha-1 blockers, such as prazosin and moxisylyte, have been investigated in randomized trials. Some studies suggest reductions in attack frequency and severity compared with placebo, but variable results, modest effects, and adverse events (hypotension, dizziness) limit their routine use (26,33).

Selective serotonin reuptake inhibitors (SSRIs), particularly fluoxetine, have been tested in controlled trials. A crossover study demonstrated that fluoxetine significantly reduced attack frequency and severity compared with nifedipine in patients with primary and secondary RP, along with improved thermographic response to cold exposure. However, larger placebo-controlled trials are lacking (34,35).

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) have been evaluated for their endothelial and vasodilatory effects. While some early studies suggested potential benefit with ARBs such as losartan, evidence is inconsistent and generally inferior to traditional therapies, ACE inhibitors may not improve and could slightly worsen attack frequency (32-34).

Topical nitrates (e.g., nitroglycerin or glyceryl trinitrate) have been examined in multiple randomized trials. Meta-analysis indicates no clear benefit on attack frequency or severity versus placebo, and systemic side effects - such as headache, hypotension, and dizziness - can limit tolerability (33,35).

Other agents such as pentoxifylline or thromboxane synthase inhibitors have been included in clinical trials but generally have not demonstrated consistent benefit in reducing RP symptoms, and their clinical use remains investigational (33,36).

Statins (e.g., atorvastatin) have also been proposed as adjunctive therapy based on endothelial protection, reduction in oxidative stress, and potential benefits in reducing digital ulcer formation, but evidence is preliminary and not incorporated into major treatment guidelines (35,37).

Overall, these alternative pharmacologic therapies may be considered in selected patients with refractory RP after failure of conventional treatments. Nevertheless, the limited and often conflicting evidence highlights the need for individualized therapeutic decision-making and further high-quality trials (36).

Botulinum Toxin in the Treatment of Raynaud's Phenomenon

Botulinum toxin (BoNT), particularly botulinum toxin type A (BoNT-A), has emerged over the past decade as a potential therapeutic option for patients with refractory Raynaud's

phenomenon (RP), especially in cases associated with systemic sclerosis (SSc) and digital ischemia. Its use is generally considered in patients who remain symptomatic despite optimized conventional vasodilator therapy or who develop ischemic complications such as digital ulcers. Recent literature consists predominantly of small randomized trials, prospective cohorts, and systematic reviews, with increasing availability of open-access publications (38-40).

Botulinum toxin A is produced by Clostridium botulinum and classically exerts its effect by inhibiting the presynaptic release of acetylcholine through cleavage of SNAP-25, thereby blocking neuromuscular transmission. In the context of RP, its mechanism is believed to extend beyond skeletal muscle relaxation and to involve modulation of sympathetic vasoconstriction (39,41).

Experimental and clinical data suggest that BoNT-A inhibits the release of norepinephrine from sympathetic nerve endings, thereby attenuating vasoconstrictive signaling in vascular smooth muscle cells (VSMCs) (6,39). Additionally, it may reduce cold-induced vasospasm by interfering with α2C-adrenoreceptor translocation and activity, which plays a central role in cold-mediated digital vasoconstriction (6).

Emerging mechanistic hypotheses also propose that BoNT-A may reduce reactive oxygen species (ROS) production within VSMCs, leading to decreased α2C-adrenoreceptor activation and reduced actin - myosin interaction, ultimately promoting vascular relaxation (6). Furthermore, botulinum toxin appears to modulate nociceptive pathways by inhibiting the release of substance P and glutamate, which may explain its beneficial effects on chronic ischemic pain frequently observed in secondary RP (40,42).

Clinical studies over the last years report heterogeneous but generally encouraging outcomes. Several prospective studies and small randomized controlled trials have demonstrated reductions in attack frequency and severity, improvement in pain scores, and enhanced digital perfusion following interdigital or peri-neurovascular injections of BoNT-A in both primary and secondary RP (38,40).

In systemic sclerosis - associated RP, improvements in digital ulcer healing and prevention of new ulcer formation have also been reported, although findings are not entirely consistent across trials (43). Some studies have failed to demonstrate significant objective improvements

in blood flow measurements (e.g., laser Doppler perfusion), despite symptomatic benefit, highlighting variability in outcome measures and patient populations (39).

A recent systematic review and meta-analysis concluded that BoNT-A may reduce pain and attack frequency in refractory RP, but emphasized the limited sample sizes, heterogeneity of injection protocols, and the need for larger, high-quality randomized trials. Overall, the certainty of evidence remains moderate to low, yet clinical experience increasingly supports its role in selected patients with severe disease (39).

Botulinum toxin is typically administered through interdigital or peri-arterial injections in the hand, targeting the neurovascular bundles. However, there is currently no standardized dosing regimen or consensus regarding dilution, injection sites, or retreatment intervals (39).

Treatment is generally well tolerated. The most frequently reported adverse effect is transient weakness of intrinsic hand muscles, which is usually mild and self-limiting (40). Other adverse events are uncommon. Nevertheless, injections must be repeated periodically due to the temporary duration of effect, typically lasting several months. Development of partial resistance has been described but appears rare (39).

Despite growing interest, several limitations remain - published studies vary substantially in patient selection (primary vs secondary RP), disease severity, injection technique, dosing, and outcome definitions, which complicates interpretation and comparison of results (38). Additionally, long-term safety data and cost-effectiveness analyses are limited.

Future research should focus on adequately powered randomized controlled trials with standardized protocols and objective vascular endpoints. Clarification of the precise molecular mechanisms of action may also help refine patient selection and optimize treatment strategies.

In summary, botulinum toxin represents a promising adjunctive therapy for refractory Raynaud’s phenomenon, particularly in systemic sclerosis-associated disease with ischemic complications. While current evidence suggests potential benefits in reducing vasospastic attacks, pain, and possibly digital ulcer burden, further high-quality studies are required before it can be incorporated into standardized treatment algorithms.

Surgical and Revascularization Approaches in Raynaud's Phenomenon

In severe and refractory Raynaud's phenomenon (RP) - particularly when digital ischemia, non-healing ulcers, or impending tissue loss persist despite optimized pharmacologic therapy - surgical and revascularization strategies are considered as adjunctive or salvage interventions aimed at restoring blood flow and interrupting pathological vasospastic mechanisms (17).

Surgical approaches in RP primarily fall into two broad categories: (1) sympathetic modulation procedures to reduce abnormal vasoconstriction by interrupting sympathetic input to the digital vasculature, and (2) direct revascularization techniques addressing discrete macrovascular occlusions contributing to chronic ischemia (17,44).

Sympathetic Modulation and Microsurgical Techniques

Sympathectomy - whether at proximal or distal levels - remains the mainstay surgical procedure for refractory RP. It is performed with the goal of reducing excessive sympathetic-mediated vasospasm that contributes to diminished digital perfusion. Microsurgical techniques, including periarterial sympathectomy and excision of sympathetic fibers around affected arteries, have been developed to target sites of most significant vasospastic contribution (44,45).

In a retrospective surgical series, patients with treatment-resistant RP who underwent microsurgical excision of sympathetic nerve fibers and adventitial stripping of affected digital arteries demonstrated significant short-term improvements in Raynaud's attack severity and duration, as well as reductions in pain scores and clinical severity indices compared with non-surgical controls. These findings support the feasibility and early efficacy of minimally invasive sympathetic modulation in selected patients (46).

A recent review highlights that peripheral sympathectomy and related neurectomy techniques have evolved with microsurgical refinement, showing promise in managing refractory RP by interrupting distal sympathetic pathways and potentially improving nutritive blood flow to the digits (44,47).

Direct Revascularization in Secondary Raynaud's Phenomenon

In patients with secondary RP, particularly when imaging demonstrates segmental occlusion of digital arteries, direct revascularization may be considered (17,48). Digital artery reconstruction using interposition vein grafts has been evaluated in a cohort of patients with chronic hand

ischemia due to discrete arterial occlusions: the majority experienced near-complete resolution of ischemic pain and ulceration, and the 5-year recurrence-free rate approached ~69 % (48).

These outcomes suggest that, when structural arterial obstruction significantly contributes to ischemia, restoring luminal continuity through vein grafting can offer durable clinical benefit beyond what can be achieved with sympathectomy alone (48).

Clinical Integration and Patient Selection

Surgical and revascularization procedures are generally reserved for patients with refractory and severe RP, who have failed optimized medical and lifestyle management and exhibit objective evidence of tissue threat or fixed macrovascular disease. Comprehensive evaluation - including angiography or vascular imaging - is essential to determine whether the pathological substrate is primarily vasospastic (favoring sympathectomy) or occlusive (favoring reconstruction) (17,48).

Importantly, these procedures should be integrated into a multidisciplinary management plan that also addresses modifiable risk factors (e.g., smoking cessation) and optimizes medical therapy to maintain long-term vascular health (17).

Dietary Supplements, Vitamins, and Nutraceuticals in Raynaud's Phenomenon

Limited randomized evidence suggests that vitamin D3 supplementation in vitamin D-deficient RP patients can improve Raynaud's symptom scores and subjective severity. In a double-blind, placebo-controlled trial, monthly high-dose oral vitamin D3 raised serum vitamin D and was associated with improved patient-reported outcomes over 8 weeks compared with placebo. This supports the idea that correcting deficiency might benefit vascular symptoms in RP (49).

Omega-3 polyunsaturated fatty acids (PUFAs), particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are proposed to improve endothelial function and reduce inflammatory mediators implicated in vasospasm. An early randomized, placebo-controlled trial investigated high-dose fish oil (approximately 3.96 g EPA + 2.64 g DHA daily) in patients

with primary Raynaud's phenomenon. After 12-17 weeks, fish oil supplementation significantly delayed the onset of cold-induced vasospasm and increased digital systolic pressures compared to placebo, suggesting enhanced vascular reactivity in response to cold challenge. However, the study predated current standards in trial design, and the effects in secondary Raynaud's remain unclear. Despite these findings, consensus guidelines do not currently endorse omega-3 supplementation specifically for Raynaud's, although dietary omega-3 intake may support general vascular health (50).

Dietary nitrate from beetroot juice (BJ) has been studied as a nutraceutical in Raynaud's phenomenon because it increases nitric oxide (NO) metabolites, which can enhance vasodilation and microvascular blood flow. In a double-blind, randomized crossover trial, chronic BJ supplementation increased thumb blood flow after cold challenge, enhanced endothelium-dependent and -independent vasodilation, improved inflammatory status, and reduced systolic and diastolic blood pressure in adults with RP compared to baseline conditions. Both nitrate-rich and nitrate-depleted BJ showed some benefits, suggesting that other bioactive beetroot components may contribute (51)

Ginkgo biloba extract has been hypothesized to improve microvascular circulation. Some small, double-blind studies have reported reduced frequency of Raynaud's episodes with high-dose Ginkgo compared to placebo in primary Raynaud's, though effects on severity and duration are inconsistent and these studies predate rigorous modern trial design standards (52).

In summary, although several supplements demonstrate biological plausibility in improving endothelial function or reducing oxidative stress, current evidence does not support their routine use as primary therapy for Raynaud's phenomenon. Most modern reviews highlight the need for well-designed, adequately powered randomized controlled trials before nutraceuticals can be incorporated into evidence-based treatment algorithms (4,13).

Discussion

Raynaud's phenomenon (RP) is a complex disorder with multifactorial pathophysiology, variable clinical presentation, and limited high-quality evidence guiding management. This review summarized non-pharmacologic strategies, first- and second-line pharmacologic therapy, prostanoids, endothelin receptor antagonists, surgical interventions, and adjunctive dietary or nutraceutical therapies.

Non-pharmacologic measures - trigger avoidance, temperature management, smoking cessation, stress reduction, and patient education - remain foundational, particularly in primary RP, and can significantly reduce attack frequency and severity (4,6).

Calcium channel blockers (CCBs) are first-line pharmacologic therapy. Meta-analyses and trials show reductions in attack frequency, duration, and severity, with dihydropyridine agents preferred due to selective peripheral vasodilation and favorable safety (4,21). PDE-5 inhibitors offer modest benefit in refractory cases, and prostanoids, primarily IV iloprost, are important for severe ischemia or digital ulcers (23,24). Endothelin receptor antagonists such as bosentan prevent new digital ulcers in secondary RP but have limited effect on established lesions or attack frequency (29). Other pharmacologic agents - including α1-blockers, SSRIs, ACE inhibitors, ARBs, nitrates, pentoxifylline, and statins - remain investigational (26,33,36).

Surgical and revascularization interventions are reserved for refractory or ischemic RP. Digital sympathectomy may reduce ischemic pain and promote ulcer healing, while angioplasty can restore flow in proximal arterial stenosis. Thoracic sympathectomy is now rarely indicated due to variable efficacy and potential adverse effects. Multidisciplinary care is essential in these complex cases (44-48).

Adjunctive nutraceuticals - vitamin D3, omega-3 fatty acids, Ginkgo biloba, dietary nitrate - have biological plausibility but lack high-quality clinical evidence and should not replace established therapies (49-51). Clinicians should monitor supplement use for potential interactions and guide realistic expectations.

Limitations and Evidence Gaps

Across all therapeutic domains, the primary limitation is the paucity of large, well-powered randomized controlled trials. Heterogeneity in patient populations (primary versus secondary RP), outcome definitions, dosing regimens, and intervention protocols complicates direct comparison and meta-analytic synthesis. Many studies are small, single-center, or observational, limiting generalizability (4,6). Long-term safety data for novel interventions such as botulinum toxin, ERAs, and prostanoids remain limited, and optimal treatment algorithms are yet to be established. In addition, objective measures of microvascular perfusion and standardized outcome reporting are inconsistently applied, further challenging interpretation (4,6,39).

Future Directions

Future research should prioritize multicenter, randomized trials with standardized definitions of RP, objective vascular endpoints, and clinically relevant outcomes including digital ulcer prevention and quality-of-life measures. Mechanistic studies exploring endothelial, neural, and inflammatory pathways may inform targeted therapies and personalized treatment selection. The integration of non-pharmacologic interventions, nutraceuticals, and pharmacologic agents in combinatory strategies also warrants rigorous evaluation. Finally, development of evidence-based guidelines for refractory RP, including invasive and surgical options, remains a high-priority need.

Conclusion

Management of Raynaud's phenomenon requires a nuanced, individualized approach that balances lifestyle interventions, first- and second-line pharmacologic therapies, and, in selected cases, invasive or adjunctive measures. While significant progress has been made in understanding the pathophysiology and expanding the therapeutic armamentarium, substantial evidence gaps persist. High-quality trials, standardized outcome reporting, and mechanistic insights are urgently needed to optimize care and improve long-term outcomes in patients with both primary and secondary RP.

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