

# Therapeutic Peptides in Orthopaedics: Applications, Challenges, and Future Directions

Omar F. Rahman, MD, MBA 

Steven J. Lee, MD

William A. Seeds, MD

## ABSTRACT

Therapeutic peptides are emerging as promising adjuncts in the management of orthopaedic injuries, grounded in their ability to modulate molecular signaling networks central to cellular medicine. By acting on key pathways such as PI3K/Akt, mTOR, MAPK, TGF- $\beta$ , and AMPK, peptides exert influence over tissue regeneration, inflammation resolution, and neuromuscular recovery. Wound-healing peptides such as BPC-157, TB-500, and GHK-Cu promote angiogenesis, integrin-mediated extracellular matrix remodeling, and fibroblast activation, whereas growth hormone secretagogues like ipamorelin, CJC-1295, tesamorelin, sermorelin, and AOD-9604 activate IGF-1 signaling and satellite cell repair. Recovery-enhancing agents such as epithalon, delta sleep-inducing peptide, and pinealon target circadian and mitochondrial regulators, and neuroactive peptides like selank, semax, and dihexa enhance brain-derived neurotrophic factor and HGF/c-Met pathways critical to neuroplasticity. Although preclinical studies are promising, there is a current lack of clinical trials. This review integrates current mechanistic insights with orthopaedic relevance, emphasizing safety, efficacy, and future directions for responsible integration into musculoskeletal care.

From the Pacific Coast Sports Medicine, Los Angeles, CA (Dr. Rahman); Lenox Hill Hospital, New York Orthopedics, New York, NY (Dr. Lee); and the Redox Medical Group, Beverly Hills, CA (Dr. Seeds).

Correspondence to Dr. Rahman:  
omarrahman1@gmail.com

None of the following authors or any immediate family member has received anything of value from or has stock or stock options held in a commercial company or institution related directly or indirectly to the subject of this article: Rahman, Lee, and Seeds.

*JAAOS Glob Res Rev* 2026;10: e25.00236

DOI: 10.5435/JAAOSGlobal-D-25-00236

Copyright 2025 The Authors. Published by Wolters Kluwer Health, Inc. on behalf of the American Academy of Orthopaedic Surgeons. This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

**T**he therapeutic era of peptides began in 1921 with the discovery of insulin, a breakthrough that revolutionized diabetes and helped establish biologic therapies in medicine<sup>1</sup> Since then, peptide hormones like oxytocin and human growth hormone (GH) have entered clinical use, and glucagon-like peptide-1 (GLP-1) receptor agonists such as semaglutide are now widely prescribed for obesity and metabolic disease—conditions increasingly recognized for their effect on orthopaedic outcomes. Before elective orthopaedic surgery, it is recommended to discontinue GLP-1 medications as they can delay gastric emptying and increase aspiration risk during anesthesia.

Peptides are short chains of amino acids that act as precise messengers in the body's communication system across various physiological systems according to cellular medicine principles. These molecules play a role in controlling molecular pathways related to metabolism efficiency, immune modulation, balance of

oxidative stress, and regeneration of tissues. Their capacity to influence communication processes like PI3k/Akt, MAPK, NF-κB, and AMPk makes them tools, for improving cellular function and resilience.

Although peptides have been used systemically for decades, their application in orthopaedics—particularly for tendon healing, cartilage repair, and muscle recovery—has only recently gained attention.<sup>2-5</sup> Growing patient interest, especially among wellness-focused individuals and athletes, has contributed to this shift. At the same time, a number of researchers are actively exploring these therapies to better understand their role in musculoskeletal care. As a result, orthopaedic surgeons are increasingly asked by their patients to counsel them on the risks, benefits, and emerging data surrounding peptide-based interventions.

This review offers an evidence-informed framework for orthopaedic surgeons seeking to navigate the evolving field of therapeutic peptides. We summarize key mechanisms of action, categorize clinically relevant peptide classes, and address current limitations, including gaps in human data, safety considerations, and regulatory ambiguity. By presenting a forward-looking perspective on therapeutic peptides, we aim to support clinicians in making informed, responsible decisions and engaging in nuanced discussions with patients and colleagues alike.

## Peptides for Wound Healing

Peptides involved in tissue repair are among the most actively studied in the context of orthopaedic and regenerative medicine. They exert their therapeutic effects by modulating molecular signaling networks central to tissue regeneration. Key pathways include PI3K/Akt and MAPK, which promote fibroblast proliferation, collagen synthesis, and angiogenesis; TGF-β signaling, which or-

chestrates extracellular matrix remodeling; and NF-κB inhibition, which regulates inflammation resolution (Table 1). The peptides in this category also influence integrin-FAK signaling and eNOS-driven nitric oxide release—critical in both revascularization and immune modulation.<sup>6,7</sup> Clinically, they are being explored for their potential to accelerate postoperative recovery, support chronic soft-tissue healing, and improve tendon-to-bone integration following procedures such as rotator cuff repair and ACL reconstruction.<sup>8</sup>

## Body Protection Compound-157

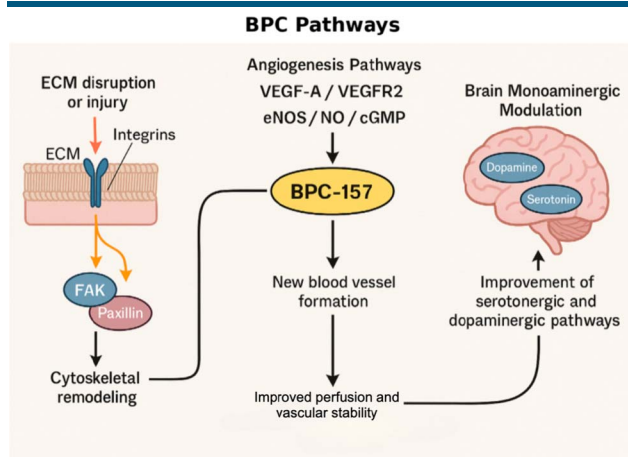
Body protection compound-157 (BPC-157) is a 15-amino-acid peptide originally derived from human gastric juice. Preclinical studies have shown regenerative potential across various tissues, including tendons, ligaments, muscle, nerves, and gastrointestinal lining.<sup>9-11</sup> Mechanistically, BPC-157 promotes fibroblast activity, modulates the nitric oxide system, enhances angiogenesis through vascular-endothelial growth factor, down-regulates proinflammatory cytokines, and stimulates collagen remodeling (Figure 1).<sup>12,13</sup> In rodent models, BPC-157 has been associated with improvements in Achilles tendon structure and biomechanical strength.<sup>14</sup> A case series of 17 patients reported reduced symptoms in more than 90% of patients following intra-articular knee BPC-157 injections for tendon and ligament injuries at minimum of 6-month follow-up.<sup>15</sup> BPC-157 is usually injected subcutaneously or intramuscularly with some practitioners injecting just proximal to the injured site for maximal benefit. Because it is natively found in the gastric mucosa, BPC-157 can also be taken orally, although bioavailability is less than if injected.

A related compound, pentadecapeptide arginate, is a stabilized form of BPC-157, designed to enhance bioavailability and shelf-life. Although pentadecapeptide arginate’s angiogenic properties support its regenerative

**Table 1. Wound Healing Therapeutic Peptides and Molecular Pathways**

Peptide/Class	Mechanisms of Action	Primary Molecular Pathways
BPC-157	Angiogenesis, ECM remodeling, NO signaling, integrin modulation	PI3K/Akt, VEGF, eNOS, TGF-β, FAK
TB-500	Cell migration, inflammation modulation, cytoskeletal repair	MAPK, NF-κB, actin polymerization, FAK
GHK-Cu	Collagen turnover, antioxidant defense, matrix regeneration	MMP regulation, NRF2, copper-redox axis

BPC = body protection compound, ECM = extracellular matrix, TB = thymosin beta, GHK-Cu = glycine-histidyl-lysine-copper, NO = nitric oxide, PI3K = phosphoinositide 3-kinase, AKT = protein kinase B, VEGF = vascular endothelial growth factor, eNOS = endothelial nitric oxide synthase, TGF-β = transforming growth factor-beta, FAK = focal adhesion kinase, MAPK = mitogen-activated protein kinase, NF-κB = nuclear factor kappa light chain enhancer of activated B cells, MMP = matrix metalloproteinases, NRF2 = nuclear factor erythroid 2-related factor 2.

**Figure 1**

Mechanism of action of BPC-157. BPC-157 = body protection compound-157.

effects, there is a theoretical risk regarding abhorrent tumorigenesis in dysplastic tissues. These remain speculative because this compound has also been found to inhibit tumor growth in several cell lines.<sup>16</sup> Nevertheless, it highlights the importance of continued safety monitoring, particularly as clinical interest expands.

### TB-500

TB-500 is a synthetic peptide fragment derived from thymosin beta-4 (Tβ4), an endogenous protein known to be upregulated in response to tissue injury. The active segment within TB-500 promotes actin polymerization, progenitor cell recruitment, and enhanced cellular migration—processes integral to wound healing.<sup>17,18</sup> Preclinical studies and veterinary use have suggested benefit in tendon and muscle repair, with observed anti-inflammatory effects and proangiogenic activity that mirror those of BPC-157.<sup>19,20</sup> TB-500 is usually injected subcutaneously or intramuscularly and generally has limited oral bioavailability.

### GHK-Cu

GHK-Cu is a naturally occurring copper-binding tripeptide involved in skin and connective tissue remodeling. It stimulates dermal fibroblast proliferation, regulates matrix metalloproteinases, and supports collagen turnover. Widely studied in dermatologic and aesthetic medicine for its wound healing and antiaging effects, GHK-Cu is now being explored for orthopaedic applications, particularly in soft-tissue regeneration and scar modulation.<sup>21,22</sup> Early studies suggest antioxidant properties and matrix turnover mechanisms that may be

relevant in acute injuries and chronic overuse conditions. GHK-Cu is generally administered subcutaneously.

## Peptides for Muscle and Cartilage Repair

Peptides that support muscle repair and cartilage regeneration are gaining attention in orthopaedics, particularly as adjuncts in both postoperative rehabilitation and performance recovery. These peptides primarily act through the GH/IGF-1 axis, which activates the PI3K/Akt/mTOR cascade—stimulating satellite cell proliferation, muscle protein synthesis, and chondrocyte matrix production.<sup>23</sup> In addition, these peptides may indirectly regulate AMPK activity to promote mitochondrial efficiency and FoxO transcription factors (Table 2). These pathways are associated with suppression of muscle atrophy and improved cartilage matrix integrity—benefits that are relevant for both high-demand athletes and aging patients with sarcopenia or osteoarthritis.<sup>7,24</sup>

### Growth Hormone Secretagogues: Ipamorelin, CJC-1295, Tesamorelin, and Sermorelin

GH secretagogues are synthetic peptides that stimulate the pituitary gland to increase endogenous growth hormone secretion. Unlike exogenous GH, they preserve the negative feedback loop, thereby minimizing suppression of natural hormone production. Ipamorelin, a selective ghrelin receptor agonist, promotes GH release by inhibiting somatostatin and is noted for its minimal off-target endocrine effects, particularly on cortisol and prolactin.<sup>25,26</sup> GH secretagogues are generally administered subcutaneously. CJC-1295, a long-acting analog of growth hormone-releasing hormone (GHRH), can be administered with or without a drug affinity compound (DAC) to modulate the timing and release of GH.<sup>27</sup> In combination, ipamorelin and CJC-1295 without DAC (also known as Modified GRF) exhibit a synergistic effect, elevating both GH and IGF-1 levels in a pulsatile, physiologic manner.<sup>28</sup> Tesamorelin, a 44-amino-acid GHRH analog, is FDA approved for HIV-related lipodystrophy and is of interest in orthopaedics due to its anabolic effects on lean body mass.<sup>29,30</sup> Similarly, sermorelin is a GHRH analog that was FDA approved for children with growth hormone deficiency. The established safety profiles of these GH secretagogues in defined populations make them particularly attractive candidates for off-label use in musculoskeletal recovery.<sup>31</sup>

GH secretagogues may activate satellite cells, promote myofibrillar protein synthesis, and help mitigate disuse atrophy during immobilization. Elevated IGF-1 levels

**Table 2. Muscle and Cartilage Repair Therapeutic Peptides and Molecular Pathways**

Peptide/Class	Mechanisms of Action	Primary Molecular Pathways
CJC-1295 + ipamorelin	Anabolism, muscle repair, chondrocyte activation	GHRH → GH → IGF-1 → PI3K/Akt/mTOR
Tesamorelin	Lean mass gain, metabolic restoration, tissue regeneration	GH/IGF-1 axis, FoxO suppression
AOD-9604	Cartilage repair, lipolysis without IGF-1 stimulation	AMPK activation, lipid metabolism

GH = growth hormone, GHRH = growth hormone releasing hormone, IGF = insulin-like growth factor, PI3K = phosphoinositide 3-kinase, AKT = protein kinase B, mTOR = mammalian target of rapamycin, FoxO = forkhead box O, AOD = anti-obesity drug, AMPK = AMP-activated protein kinase.

have been linked to enhanced chondrocyte proliferation, cartilage matrix production, and osteoblast differentiation—mechanisms that support fracture healing and joint preservation.<sup>32</sup> Although large-scale orthopaedic trials are lacking, animal studies and indirect clinical evidence provide a biologic rationale for their use. In addition, improved sleep quality, commonly associated with GH elevation, may offer ancillary recovery benefits.<sup>33</sup>

### AOD-9604

AOD-9604 is a synthetic peptide fragment of human growth hormone, originally investigated for its lipolytic effects and is generally administered subcutaneously. Unlike full-length human growth hormone, AOD-9604 promotes fat metabolism and may support cartilage repair without markedly altering glucose homeostasis or systemic IGF-1 levels.<sup>34</sup> A meta-analysis of six randomized controlled studies on the safety of AOD-9604 on humans demonstrated no effect on serum IGF-1 levels.<sup>35</sup> In a rabbit model of osteoarthritis, intra-articular injection of AOD-9604 combined with hyaluronic acid (HA) demonstrated improvements in cartilage morphology and joint surface integrity.<sup>36</sup> This peptide has been explored in some regenerative protocols for osteoarthritis, often in combination with HA or platelet-rich plasma (PRP).

Beyond postinjury recovery, these peptides may serve a role in “prehabilitation”—helping patients optimize muscle mass, tissue resilience, and joint function before surgery. They can also be used as part of injury prevention strategies in high-performance populations and for the management of age-related conditions, such as sarcopenia, osteoarthritis, or persistent tendinopathies. However, clinicians must carefully weigh these benefits against potential risks, including hormonal dysregulation and prohibited substance use for professional athletes by the World Anti-Doping Agency.<sup>2,37,38</sup> Although many of

the aforementioned peptides are banned for use by elite athletes due to potential performance-enhancing effects, they may still offer substantial therapeutic benefits for the general patient population when used judiciously under physician supervision.

## Peptides for Sleep Enhancement and Recovery Optimization

Although orthopaedic treatments typically emphasize structural repair, systemic recovery—particularly sleep regulation, hormonal balance, and stress adaptation—plays a key role in optimizing outcomes. Sleep-enhancing peptides exert systemic effects by acting on circadian regulators (e.g., CLOCK, BMAL1), restoring pineal-mitochondrial signaling, and enhancing endogenous GH release (Table 3). These mechanisms align with improvements in redox balance, hormonal cycling, and tissue regeneration—core to recovery and resilience in orthopaedic populations. These sleep-enhancing peptides are generally administered subcutaneously. Although interest in these compounds has grown within the “biohacking” and “antiaging” communities, their applications may also be relevant in orthopaedic recovery.

### Epithalon

Epithalon is a synthetic tetrapeptide derived from the pineal gland peptide, epithalamin. Originally studied in Eastern Europe, it has been associated with the regulation of melatonin production, normalization of circadian rhythms, and activation of telomerase.<sup>39,40</sup> These effects have made it a subject of interest in longevity medicine.<sup>41,42</sup> Although not directly targeting musculoskeletal tissue, epithalon’s systemic benefits, such as improved sleep quality and hormonal regulation, may indirectly support recovery by enhancing endogenous GH secretion and reducing oxidative stress.

**Table 3. Sleep and Recovery Optimization Therapeutic Peptides and Molecular Pathways**

Peptide/Class	Mechanisms of Action	Primary Molecular Pathways
Epithalon	Circadian restoration, telomere maintenance, redox tuning	SIRT1, telomerase activation, CLOCK genes
DSIP	Sleep enhancement, hormonal regulation, stress resilience	Hypothalamic GH release, mitochondrial biogenesis
Pinealon	Cognitive support, neuroprotection, sleep-wake modulation	Mitochondrial antioxidants, neuronal support

DSIP = Delta Sleep-Inducing Peptide, GH = growth hormone, SIRT1 = sirtuin 1, CLOCK = circadian locomotor output cycles kaput.

### Delta Sleep-Inducing Peptide

Delta sleep-inducing peptide is a neuropeptide found in the hypothalamus and named for its ability to promote delta wave, or slow wave, sleep in rodent studies. Some studies suggest that it may increase endogenous GH secretion and modulate stress-related hormonal responses.<sup>43</sup> Its potential benefits in postoperative recovery and sleep regulation warrant continued investigation.

### Pinealon

Pinealon is a tripeptide thought to influence neuronal metabolism and support mitochondrial function, especially in aging or stressed neural tissues. Studies have explored its potential in enhancing cognitive function, improving sleep, and promoting resilience to oxidative stress.<sup>44</sup> Its relevance in orthopaedics may lie in its ability to support cognitive recovery and psychological well-being—factors that can improve rehabilitation and patient-reported outcomes postoperatively.

### Peptides for Neurological Recovery and Mind-Muscle Connectivity

Although orthopaedic rehabilitation emphasizes the mechanical restoration of joints, tendons, and muscles, the central and peripheral nervous systems are increasingly recognized as important drivers in recovery. Neuroactive peptides work through mechanisms such as

brain-derived neurotrophic factor (BDNF) upregulation, HGF/c-Met signaling, and modulation of monoamine neurotransmitters (Table 4). These peptides are generally administered subcutaneously and intranasally. These support neuroplasticity, synaptogenesis, and cortical integration of motor control—all essential for neuromuscular rehabilitation and mind-muscle connectivity in prolonged orthopaedic recovery.

### Selank

Selank is a synthetic heptapeptide based on the immunomodulatory molecule tuftsin and approved in Russia for the treatment of anxiety.<sup>45</sup> It modulates neurotransmitters such as serotonin and dopamine and may increase levels of BDNF, a key molecule associated with synaptic plasticity and emotion regulation.<sup>46</sup> Within orthopaedic recovery, selank's anxiolytic and neurotrophic effects may help patients maintain psychological resilience, optimize mental clarity, and participate more actively in rehabilitation protocols.<sup>47</sup>

### Semax

Semax is a synthetic neuropeptide derived from adrenocorticotrophic hormone and has been used in Russia for a range of neurological conditions, including ischemic stroke and optic nerve injury.<sup>48</sup> It exerts neuroprotective and neurotrophic effects, including BDNF upregulation and synaptogenesis.<sup>49</sup> In orthopaedics, semax may be

**Table 4. Neuroactive Therapeutic Peptides and Molecular Pathways**

Peptide/Class	Mechanisms of Action	Primary Molecular Pathways
Selank	Functional anxiolysis, synaptic plasticity, immune modulation	BDNF, serotonin/Dopamine, TrkB
Semax	Neurogenesis, cognitive resilience, neuroprotection	BDNF, TrkB, anti-inflammatory genes
Dihexa	Synaptogenesis, neurorepair, neuromuscular connectivity	HGF/c-met signaling

BDNF = brain-derived neurotrophic factor, TrkB = tropomyosin receptor kinase B, HGF = hepatocyte growth factor, c-met = c mesenchymal-epithelial transition factor.

useful in select cases involving prolonged neuromuscular retraining or peripheral nerve recovery such as brachial plexopathies. In addition, its reported effects on attention and mental stamina could indirectly support compliance in complex rehabilitation regimens.

### Dihexa

Dihexa is a peptide originally developed to target cognitive decline in neurodegenerative diseases. It potentiates hepatocyte growth factor activity and stimulates the c-Met receptor pathway—mechanisms associated with synaptogenesis and neural remodeling.<sup>50</sup> Preclinical studies have shown restoration of memory function and enhanced synaptic connectivity in Alzheimer models.<sup>51</sup> Dihexa mechanism of action suggests potential for enhancing the mind-muscle connection.

### Considerations for Clinical Adoption: Evidence, Safety, and Regulatory Landscape

Despite encouraging preclinical findings and increasing patient enthusiasm, the integration of peptide-based therapies in mainstream orthopaedic practice remains cautious. This is understandable, as the field continues to prioritize data from double-blind, placebo-controlled, randomized, controlled trials (RCTs) as the benchmark for therapeutic adoption. Key considerations—such as emerging clinical data, variability in product quality, and evolving regulatory oversight—highlight the importance of careful, evidence-based implementation.<sup>52</sup> Nonetheless, ongoing research and clinical use within cellular and regenerative medicine are steadily contributing to the broader understanding of these agents.

### Emerging Clinical Data

It is crucial to understand that peptide-based treatments have already gained credibility in real-world applications. GLP-1 receptor agonists like semaglutide and GHRH analogues such as tesamorelin have received the FDA's stamp of approval with evidence from studies backing them up. These remedies not only improve metabolism but also play a role in tissue regeneration, mitochondrial efficiency, and immune system adjustments—showcasing the broad implications of focusing efforts toward cellular signaling pathways such as AMPK, PI3K/AKT, and mTOR. Numerous experimental peptides currently undergoing clinical and preclinical research target pathways in the body. As knowledge grows about these peptides and their effects,

it becomes apparent that both established and new peptides share similar molecular pathway modulation underscoring the importance of the processes they affect. In the fields of regenerative medicine, there is a moment approaching where adopting cellular medicine could lead to effective and proven approaches, for healing, recovery, and lasting functional improvements.

### Limitations in Clinical Evidence and Trial Design

The current orthopaedic literature on peptides is dominated by animal models, small prospective cohorts, and case series, with very limited RCTs. This gap is especially pronounced for musculoskeletal end points such as tendon-to-bone healing and cartilage repair. As such, any clinical use should be framed as exploratory and hypothesis generating rather than standard of care. RCTs should be adequately powered with defined orthopaedic indications. Primary endpoints should center on pain and function Knee Injury and Osteoarthritis Outcome Score (KOOS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Patient-Reported Outcome Measurement Information System (PROMIS) scores), structure (MRI evaluation with delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) when appropriate), and time to milestones (return to sport). Comparators should be condition specific (placebo saline, HA, or PRP) and descriptions of the peptide formulation, dose, route of administration, and schedule should be clearly defined. Trial design and data sharing of standardized protocol elements and outcomes should be encouraged to support reproducibility of outcomes and meta-analysis. In addition, examples from other biologic therapies, such as growth factors and gene therapy, that showed early promise but failed clinical translation underscore the importance of rigorous study design, safety monitoring, and realistic expectations in peptide research.

### Safety Concerns

Therapeutic peptides are generally considered safe with low immunogenicity and a favorable adverse effect profile compared with many pharmacologic agents. Among the most frequently reported adverse effects are minor and self-limiting such as local injection site erythema, transient hormonal shifts, and receptor desensitization with prolonged or high-frequency use.<sup>3,4</sup> For clinicians and patients alike, safety is the first and most pressing concern, especially given the association of peptides with performance enhancement and off-label use. It is important to note that peptides often demonstrate

pleiotropic effects, influencing multiple physiologic pathways beyond their target tissue. Although this may offer systemic recovery and healing benefits, it introduces complexity in predicting responses—especially in polypharmacy and comorbidity contexts. The current body of clinical experience suggests that these compounds are well tolerated when prescribed with proper clinical oversight. Still, formal large-scale safety studies will be essential to solidify best practices. Safety monitoring should include immunogenicity, endocrine panels for GH-axis agents, and pharmacovigilance reporting. One of the most notable barriers to clinical translation is the lack of standardized dosing protocols across studies and clinical practices. Current literature reveals wide variation in route of administration, dose intensity, treatment duration, and frequency, even for the same peptide. BPC-157 has been administered at doses ranging from 200 mcg to 1000 mcg/day in various regimens without consensus on therapeutic thresholds. This methodological heterogeneity complicates both interstudy comparisons and the development of clinical guidelines. Establishing consensus on dosing parameters and administration techniques through standardized protocols is a necessary step toward reproducibility and regulatory approval (Table 5).

### Patient Expectations

The growing popularity of peptides, fueled in part by wellness social media influencers and anecdotal success stories, has led some patients to pursue these therapies independently, often without clinical oversight. Misconceptions are common; patients may expect rapid healing or nonsurgical solutions for chronic or severe injuries. This age of misinformation presents a challenge for orthopaedic surgeons, who must balance evidence-based guidance with growing public interest. Providers

play a crucial role in aligning patient expectations with the current data while helping to ensure safe and appropriate use of peptides.

### Quality Control and Sourcing

Quality assurance remains a critical issue in peptide therapeutics. Although some compounding pharmacies meet high manufacturing standards and submit to third-party testing, variability in purity, potency, and sterility persists, especially among unregulated, direct-to-consumer online sources. Common problems include inconsistent dosing, label discrepancies, and endotoxin contaminants like lipopolysaccharides, which can provoke systemic inflammation. To navigate these risks, clinicians should prioritize transparent suppliers and verify product quality directly. These suppliers should be regularly inspected by the FDA and follow current Good Manufacturing Practices (cGMP). cGMP compliance ensures rigorous standards of raw material sourcing of the active pharmaceutical ingredient, potency verification, endotoxin testing, and environmental monitoring. Physicians should vet their compounding partners by requesting certificates of analysis for each lot and ensuring third-party sterility and endotoxin testing. As the therapeutic peptide market grows, sourcing from transparent, cGMP-compliant partners is essential to protect patient safety and preserve credibility in clinical use.

### Regulatory Status, Compounding Practices, and Ethical Oversight

Therapeutic peptides represent a convergence point between orthopaedic regeneration and cellular medicine. By restoring key intracellular signaling pathways, enhancing mitochondrial function, and reducing maladaptive inflammatory cycles, peptides may offer

**Table 5. Peptide Minimum Reporting Standards**

Domain	Details to Report
Molecule identification	Peptide sequence, manufacturer/source; lot number; COA
Analytical quality and sterility	Purity; assay method; sterility test; endotoxin testing; particulate testing
Formulation and stability	Reconstitution vehicle and final concentration; storage conditions
Administration plan	Route, dose, schedule, loading vs maintenance, injection technique
Concomitant therapies	Co-interventions and timing relative to peptide
Adherence and deviations	Compliance checks, missed doses, protocol deviations and reasons
Safety monitoring	Safety labs and monitoring plan, criteria for discontinuation

COA = certificate of analysis.

orthopaedic surgeons a powerful therapeutic adjunct. Clinical judgment and research rigor will be critical in translating these molecular insights into standardized care. At present, most the peptides in this review are not FDA-approved for orthopaedic indications. Clinical investigation to support new uses generally requires an Investigational New Drug (IND) application with appropriate chemistry, manufacturing, and controls, nonclinical safety, and human data. Claims of treatment benefit should not be made outside approved labeling or an institutional review board–approved protocol. If offering peptides outside approved indications, clinicians should present use as experimental, disclose regulatory status and paucity of clinical studies, describe known and unknown risks, and outline standard treatment alternative (e.g. physical therapy, NSAIDs, PRP, HA, and surgery). Institutional review board oversight or participation in a prospective registry is encouraged to systematically track outcomes and adverse events.

The regulatory framework for therapeutic peptides in the United States is dynamic. Although some peptides like tesamorelin have received formal FDA approval, many others fall under compounding provisions of the Federal Food, Drug, and Cosmetic Act—503A (patient-specific prescriptions by state-licensed pharmacies) and 503B (FDA-regulated outsourcing facilities operating under cGMP). Recent FDA actions include interim category lists that restrict or preclude the use of certain bulk drug substances in compounding unless the active pharmaceutical ingredient is listed or the product is being studied under an IND.<sup>53</sup> The regulatory trajectory of peptides may shift depending on the priorities of current FDA leadership and federal health initiatives. Renewed attention to the longevity, performance enhancement, and wellness industries has led to discussions about creating clearer pathways for legitimate development of promising peptides. Nonetheless, clinicians should verify the real-time status of specific peptides with FDA and avoid research use–only products for patient care. For athletes, potential antidoping restrictions of World Anti-Doping Agency–prohibited substances should be thoroughly discussed. Although it is plausible that select peptides may enter formal clinical trials under an IND or through fast-track orphan designation pathways, this measured approach allows innovation to move forward without compromising ethics, compliance, or patient safety. Until formal regulatory guidance is established, any use of therapeutic peptides must be supported by rigorous patient consent

protocols, proper sourcing from 503B facilities, and continued outcome tracking.

## Conclusion

Therapeutic peptides represent a promising yet evolving area in orthopaedics. Their biologic activity is supported by decades of foundational cellular medicine research and growing clinical interest. Preclinical studies have shown potential benefits in wound healing, muscle recovery, and neurocognitive support; however, these findings have not yet been consistently replicated in human trials. Current clinical use—particularly within sports medicine and regenerative medicine practices—is largely based on case reports, anecdotal experience, and mechanistic rationale rather than large-scale randomized controlled trials. Concerns around pleiotropic activity, sourcing variability, and regulatory guidance are valid and underscore the need for ongoing safety monitoring and thoughtful application. Informed, evidence-based dialogue with patients remains essential, particularly in an era where public interest and commercial marketing have outpaced peer-reviewed data.

Orthopaedic surgeons should lead clinical peptide research while using standard evidence alongside new sources to advance the field responsibly. Surgeons who join collaborative research projects and participate in multidisciplinary discussions will help determine the correct applications of peptides in musculoskeletal treatment. Professional peptide societies together with continuing medical education courses and ongoing clinical trials serve as essential components for translating peptides into validated treatment options.

Peptides are currently undergoing critical evaluation for their potential to induce epigenetic adaptations, restore metabolic flexibility, and enhance cellular efficiency. These signaling molecules activate biological pathways, which cells have used to respond to trauma, injury, and surgical metabolic stress. By influencing gene expression and optimizing intracellular communication, peptide therapeutics embody the power of cellular medicine to improve healing, resilience, and outcomes across aging, injury, and surgical recovery. We now have the opportunity to strengthen the bridge between orthopaedic restorative care and cellular medicine—an alliance that redefines what's possible for the future of musculoskeletal health. If pursued with scientific rigor, integrity, and a commitment to continuous learning, peptide therapeutics may become a valuable addition to the modern orthopaedic surgeon's toolkit.

## References

- Banting FG, Best CH, Collip JB, Campbell WR, Fletcher AA: Pancreatic extracts in the treatment of diabetes mellitus. *Can Med Assoc J* 1922;12:141-146.
- DeFoor MT, Dekker TJ: Injectable therapeutic peptides—An adjunct to regenerative medicine and sports performance? *Arthroscopy* 2025;41:150-152.
- Fosgerau K, Hoffmann T: Peptide therapeutics: Current status and future directions. *Drug Discov Today* 2015;20:122-128.
- Wang L, Wang N, Zhang W, et al: Therapeutic peptides: Current applications and future directions. *Signal Transduction Targeted Ther* 2022;7:48.
- Anand U, Bandyopadhyay A, Jha NK, Pérez de la Lastra JM, Dey A: Translational aspect in peptide drug discovery and development: An emerging therapeutic candidate. *Biofactors* 2023;49:251-269.
- König D, Kohl J, Jerger S, Centner C: Potential relevance of bioactive peptides in sports nutrition. *Nutrients* 2021;13:3997.
- Liu Q, Jia Z, Duan L, Xiong J, Wang D, Ding Y: Functional peptides for cartilage repair and regeneration. *Am J Transl Res* 2018;10:501-510.
- Gwyer D, Wragg NM, Wilson SL: Gastric pentadecapeptide body protection compound BPC 157 and its role in accelerating musculoskeletal soft tissue healing. *Cell Tissue Res* 2019;377:153-159.
- Duzel A, Vlainic J, Antunovic M, et al: Stable gastric pentadecapeptide BPC 157 in the treatment of colitis and ischemia and reperfusion in rats: New insights. *World J Gastroenterol* 2017;23:8465-8488.
- Grgic T, Grgic D, Drmic D, et al: Stable gastric pentadecapeptide BPC 157 heals rat colovesical fistula. *Eur J Pharmacol* 2016;780:1-7.
- Pevec D, Novinscak T, Brcic L, et al: Impact of pentadecapeptide BPC 157 on muscle healing impaired by systemic corticosteroid application. *Med Sci Monit* 2010;16:BR81-BR88.
- Seiwerth S, Brcic L, Vuletic LB, et al: BPC 157 and blood vessels. *Curr Pharm Des* 2014;20:1121-1125.
- Seiwerth S, Rucman R, Turkovic B, et al: BPC 157 and standard angiogenic growth factors. Gastrointestinal tract healing, lessons from tendon, ligament, muscle and bone healing. *Curr Pharm Des* 2018;24:1972-1989.
- Staresinic M, Sebecic B, Patrij L, et al: Gastric pentadecapeptide BPC 157 accelerates healing of transected rat achilles tendon and in vitro stimulates tendocytes growth. *J Orthop Res* 2003;21:976-983.
- Lee E, Padgett B: Intra-articular injection of BPC 157 for multiple types of knee pain. *Altern Ther Health Med* 2021;27:8-13.
- Radeljak S, Seiwerth S, Sikiric P: BPC 157 inhibits cell growth and VEGF signalling via the MAPK kinase pathway in the human melanoma cell line. *Melanoma Res* 2004;14:A14-A15.
- Yarmola EG, Klimenko ES, Fujita G, Bubb MR: Thymosin beta4: Actin regulation and more. *Ann N Y Acad Sci* 2007;1112:76-85.
- Gonzalez-Franquesa A, Stocks B, Borg ML, et al: Discovery of thymosin β4 as a human exerkine and growth factor. *Am J Physiol Cell Physiol* 2021;321:C770-C778.
- Goldstein AL, Hannappel E, Sosne G, Kleinman HK: Thymosin β4: A multi-functional regenerative peptide. Basic properties and clinical applications. *Expert Opin Biol Ther* 2012;12:37-51.
- Philp D, Goldstein AL, Kleinman HK: Thymosin beta4 promotes angiogenesis, wound healing, and hair follicle development. *Mech Ageing Dev* 2004;125:113-115.
- Pickart L: The human tri-peptide GHK and tissue remodeling. *J Biomater Sci Polym Ed* 2008;19:969-988.
- Wang X, Liu B, Xu Q, et al: GHK-Cu-liposomes accelerate scald wound healing in mice by promoting cell proliferation and angiogenesis. *Wound Repair Regen* 2017;25:270-278.
- Junnila RK, List EO, Berryman DE, Murrey JW, Kopchick JJ: The GH/IGF-1 axis in ageing and longevity. *Nat Rev Endocrinol* 2013;9:366-376.
- Geusens PP, Boonen S: Osteoporosis and the growth hormone-insulin like growth factor axis. *Horm Res* 2002;58(suppl 3):49-55.
- Beck DE, Sweeney WB, McCarter MD; Ipamorelin 201 Study Group: Prospective, randomized, controlled, proof-of-concept study of the ghrelin mimetic ipamorelin for the management of postoperative ileus in bowel resection patients. *Int J Colorectal Dis* 2014;29:1527-1534.
- Raun K, Hansen BS, Johansen NL, et al: Ipamorelin, the first selective growth hormone secretagogue. *Eur J Endocrinol* 1998;139:552-561.
- Teichman SL, Neale A, Lawrence B, Gagnon C, Castaigne JP, Frohman LA: Prolonged stimulation of growth hormone (GH) and insulin-like growth factor I secretion by CJC-1295, a long-acting analog of GH-releasing hormone in healthy adults. *J Clin Endocrinol Metab* 2006;91:799-805.
- Stanley TL, Chen CY, Branch KL, Makimura H, Grinspoon SK: Effects of a growth hormone-releasing hormone analog on endogenous GH pulsatility and insulin sensitivity in healthy men. *J Clin Endocrinol Metab* 2011;96:150-158.
- Stanley TL, Feldpausch MN, Oh J, et al: Effect of tesamorelin on visceral fat and liver fat in HIV-Infected patients with abdominal fat accumulation: A randomized clinical trial. *JAMA* 2014;312:380-389.
- Falutz J, Mamputu JC, Potvin D, et al: Effects of tesamorelin (TH9507), a growth hormone-releasing factor analog, in human immunodeficiency virus-infected patients with excess abdominal fat: A pooled analysis of two multicenter, double-blind placebo-controlled phase 3 trials with safety extension data. *J Clin Endocrinol Metab* 2010;95:4291-4304.
- Clemmons DR, Miller S, Mamputu JC: Safety and metabolic effects of tesamorelin, a growth hormone-releasing factor analogue, in patients with type 2 diabetes: A randomized, placebo-controlled trial. *PLoS One* 2017;12:e0179538.
- Nakasaki M, Yoshioka K, Miyamoto Y, Sasaki T, Yoshikawa H, Itoh K: IGF-I secreted by osteoblasts acts as a potent chemotactic factor for osteoblasts. *Bone* 2008;43:869-879.
- Obál F Jr, Krueger JM. GHRH and sleep. *Sleep Med Rev.* 2004;8:367-377.
- Heffernan MA, Jiang WJ, Thorburn AW, Ng FM: Effects of oral administration of a synthetic fragment of human growth hormone on lipid metabolism. *Am J Physiol Endocrinol Metab* 2000;279:E501-E507.
- Stier H: Safety and tolerability of the hexadecapeptide AOD9604 in humans. *J Endocrinol Metab* 2013;3:7-15.
- Kwon DR, Park GY. Effect of intra-articular injection of AOD9604 with or without hyaluronic acid in rabbit osteoarthritis model. *Ann Clin Lab Sci.* 2015;45(4):426-432.
- He L, Feng D, Guo H, et al: Pharmacokinetics, distribution, metabolism, and excretion of body-protective compound 157, a potential drug for treating various wounds, in rats and dogs. *Front Pharmacol* 2022;13:1026182.
- Judák P, Esposito S, Coppieters G, Van Eenoo P, Deventer K: Doping control analysis of small peptides: A decade of progress. *J Chromatogr B Analyt Technol Biomed Life Sci* 2021;1173:122551.
- Korkushko OV: The results of 30-month use of thymalin and epithalamin in people with the manifestations of an accelerated aging, in *International Symposium, Gerontological Aspects of Peptide Regulation of Organism Functions*. St. Petersburg, Nauka, 1996.

40. Korkushko O, Khavinson VK, Shatilo VB, Antonyuk-Shcheglova IA: Geroprotective effect of epithalamine (pineal gland peptide preparation) in elderly subjects with accelerated aging. *Bull Exp Biol Med* 2006;142: 356-359.
41. Khavinson V, Diomedea F, Mironova E, et al: AEDG peptide (Epitalon) stimulates gene expression and protein synthesis during neurogenesis: Possible epigenetic mechanism. *Molecules* 2020;25:609.
42. Khavinson V, Bondarev I, Butyogov A: Epithalon peptide induces telomerase activity & telomere 1 elongation in human somatic cells. *Bull Exp Biol Med* 2003;125:590-592.
43. Afaghi A, O'Connor H, Chow C: Acute effects of the very low carbohydrate diet on sleep indices. *Nutr Neurosci* 2008;11:146-154.
44. Bashkireva A, Artamonova V: The peptide correction of neurotic disorders among professional truck-drivers. *Adv Gerontol* 2012;25: 718-728.
45. Seredenin SB, Kozlovskaya MM, Blednov IA, et al: The anxiolytic action of an analog of the endogenous peptide tuftsin on inbred mice with different phenotypes of the emotional stress reaction [in Russian]. *Zh Vyssh Nerv Dejatel Im I P Pavlova* 1998;48:153-160.
46. Mjasoedov NF, Andreeva LA, Grigorjeva ME, Obergan TY, Shubina TA, Lyapina LA: The influence of selank on the parameters of the hemostasis system, lipid profile, and blood sugar level in the course of experimental metabolic syndrome. *Dokl Biol Sci* 2014;458: 267-270.
47. Vyunova T, Andreeva L, Shevchenko K, Myasoedov N: Peptide-based anxiolytics: The molecular aspects of heptapeptide selank biological activity. *Protein Pept Lett* 2018;25:914-923.
48. Inozemtsev AN, Bokieva SB, Karpukhina OV, Gumargalieva KZ, Kamensky AA, Myasoedov NF: Semax prevents learning and memory inhibition by heavy metals. *Dokl Biol Sci* 2016;468:112-114.
49. Dolotov OV, Karpenko EA, Inozemtseva LS, et al: Semax, an analog of ACTH(4-10) with cognitive effects, regulates BDNF and trkB expression in the rat hippocampus. *Brain Res* 2006;1117:54-60.
50. Wright JW, Harding JW: The brain hepatocyte growth factor/c-Met receptor system: A new target for the treatment of Alzheimer's disease. *J Alzheimers Dis* 2015;45:985-1000.
51. Benoist CC, Kawas LH, Zhu M, et al: The procognitive and synaptogenic effects of angiotensin IV-derived peptides are dependent on activation of the hepatocyte growth factor/c-met system. *J Pharmacol Exp Ther* 2014;351:390-402.
52. Lamers C. Overcoming the shortcomings of peptide-based therapeutics. *Future Drug Discov.* 2022;4(1):FDD75. doi:10.4155/fdd-2022-0009.
53. *Bulk drug substances under category 2 of the interim policies.* FDA, 2024. <https://www.fda.gov/drugs/human-drug-compounding/certain-bulk-drug-substances-use-compounding-may-present-significant-safety-risks>