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Review Article

Emerging Peptide Therapies in Orthopaedics: Evidence, Safety, and Perioperative Implications

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Background

Peptide therapies have rapidly entered musculoskeletal and orthopaedic care through direct-to-consumer performance clinics and widespread online promotion. Agents such as BPC-157 and thymosin beta-4 derivatives (TB-500) are increasingly used by patients seeking accelerated recovery, despite uncertain efficacy and limited perioperative safety data.

Questions/Purposes

This scoping review aimed to characterize the available evidence regarding commonly used peptide therapies relevant to musculoskeletal pathology and to examine safety considerations and perioperative implications for orthopaedic surgical patients, with emphasis on total joint arthroplasty (TJA).

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Conflicts of Interest Statement for Dr. Ahmed Siddiqi

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Methods

A scoping review was performed using searches of PubMed/MEDLINE, Cochrane CENTRAL, and ClinicalTrials.gov from database inception through the final search date. Studies were selected based on translational relevance to musculoskeletal healing, orthopaedic recovery, and perioperative decision-making. Eligible evidence included preclinical animal studies, mechanistic investigations, and human clinical reports. Given heterogeneity in formulations and outcome reporting, findings were summarized using structured narrative synthesis rather than quantitative pooling.

Results

The evidence base was dominated by preclinical and mechanistic studies, with limited human clinical outcome data. BPC-157 was the most frequently represented agent, with experimental models suggesting activity involving angiogenesis, inflammatory modulation, and collagen remodeling, but minimal clinical evidence applicable to orthopaedic surgery. Thymosin beta-4 derivatives, GHK-Cu, and endocrine-active agents such as growth hormone secretagogues and IGF-1 analogs demonstrated biologic plausibility but lacked robust orthopaedic outcome data. No high-quality studies directly evaluated perioperative outcomes such as wound complications, hematoma formation, infection risk, or implant-related outcomes in patients undergoing TJA. Unregulated sourcing introduces concerns regarding formulation variability and sterility.

Conclusions

Peptide therapies are increasingly encountered in orthopaedic practice, yet evidence supporting clinical efficacy and perioperative safety remains limited. In TJA, where wound complications and periprosthetic joint infection carry devastating consequences, uncertainty in product integrity and absence of validated safety data warrant a conservative perioperative approach. Future research should prioritize verified formulations, prospective registries, and clinically meaningful endpoints.

INTRODUCTION

Peptide therapies have rapidly entered mainstream musculoskeletal culture, driven by social media promotion, direct-to-consumer wellness and optimization clinics, and the expanding commercialization of biologic optimization (Vasireddi et al. 2025). Compounds such as BPC-157 and thymosin beta-4 derivatives, commonly marketed as TB-500, are increasingly used by athletes and patients seeking accelerated recovery from tendon injury, ligament reconstruction, cartilage pathology, and postoperative rehabilitation (Vasireddi et al. 2025; Mayfield et al. 2026). Despite widespread adoption, these agents are not approved by the U.S. Food and Drug Administration (FDA) for musculoskeletal indications, and the evidence supporting clinical efficacy is limited. Recent orthopaedic literature has emphasized that clinical exposure to BPC-157 has expanded far more rapidly than scientific validation, with published studies overwhelmingly consisting of preclinical models and only sparse human data (Vasireddi et al. 2025; Mayfield et al. 2026; Matek et al. 2026).

The implications of this trend extend beyond sports medicine. Orthopaedic surgery is uniquely sensitive to small shifts in perioperative risk, particularly in implant-based procedures where complications carry disproportionate consequences. In total joint arthroplasty (TJA), wound complications, hematoma formation, and delayed drainage substantially increase susceptibility to periprosthetic joint infection (PJI), an outcome associated with revision surgery, prolonged antimicrobial therapy, and durable functional decline (Xiong et al. 2025; Almeida et al. 2021). In this context, even modest alterations in angiogenesis, inflammatory signaling, or coagulation balance, as well as contamination exposure, may be clinically meaningful. Unlike conventional supplements, many peptides are administered through subcutaneous or intramuscular injection, often obtained through nonregulated sources with uncertain sterility, concentration accuracy, and compositional reliability (L. Wang et al. 2022). Product integrity may therefore represent a dominant perioperative concern independent of pharmacologic effect.

The scientific literature describing BPC-157 and thymosin beta-4 has proposed mechanistic effects on angiogenesis, inflammatory signaling, fibroblast migration, and collagen remodeling (Vasireddi et al. 2025; Mayfield et al. 2026). Other peptide agents such as GHK-Cu are marketed for wound healing and connective tissue repair, while growth hormone secretagogues and IGF-1 analogs are increasingly used in performance settings and may plausibly influence recovery physiology through systemic endocrine pathways (Pickart and Margolina 2018). However, the available data remain heterogeneous, frequently reliant on surrogate endpoints, and rarely tested in clinical settings reflective of orthopaedic surgical care (Rahman et al. 2026). Existing reviews have further highlighted that pharmacokinetic and safety characterization in humans remains incomplete, complicating clinical counseling regarding timing of discontinuation, perioperative risk stratification, and postoperative resumption (Rahman et al. 2026).

As patient use accelerates, orthopaedic surgeons are increasingly asked to counsel individuals who view peptide exposure as responsible health optimization. The absence of clinical guidelines leaves surgeons navigating an evidence gap with potential medicolegal implications, particularly when patients undergo elective procedures where the acceptable tolerance for unmeasured risk is low. Therefore, the purpose of this scoping review is to characterize the current evidence base for peptide therapies relevant to musculoskeletal care, with emphasis on BPC-157, thymosin beta-4 derivatives, and related agents, and to define safety considerations and perioperative implications for orthopaedic surgical patients, including those undergoing TJA.

MATERIALS AND METHODS

STUDY DESIGN

A scoping review was performed to map the available evidence regarding peptide therapies relevant to musculoskeletal care, including agents not approved for musculoskeletal indications and orthopaedic surgery. A scoping approach was selected given the anticipated heterogeneity of study designs, the predominance of preclinical literature, and the limited volume of human clinical outcome data. Reporting followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) where applicable, with emphasis on transparent identification of available evidence rather than quantitative pooling.

SEARCH STRATEGY

A comprehensive search of PubMed/MEDLINE and the Cochrane Central Register of Controlled Trials (CENTRAL) was performed from database inception through the final search date. ClinicalTrials.gov was queried to identify registered or ongoing trials. Search terms combined peptide agent names with musculoskeletal and perioperative keywords and included BPC-157, body protection compound, pentadecapeptide, thymosin beta-4, TB-500, TB500, GHK-Cu, copper tripeptide, growth hormone secretagogue, CJC-1295, ipamorelin, sermorelin, IGF-1, insulin-like growth factor, collagen peptide, tendon, ligament, cartilage, osteoarthritis, fracture healing, wound healing, perioperative, arthroplasty, total hip arthroplasty, total knee arthroplasty, and total joint arthroplasty. Reference lists of included articles and relevant reviews were manually screened to identify additional pertinent studies.

STUDY IDENTIFICATION AND SELECTION APPROACH

The initial search yielded a large body of literature across peptide agents and clinical domains. After removal of clearly nonrelevant records based on title and abstract screening, approximately 40 to 70 studies were identified as potentially relevant to musculoskeletal biology, orthopaedic care, or perioperative considerations. Full-text review was subsequently performed, with approximately 20 to 35 studies informing the final narrative synthesis.

Screening was performed by the authors with an emphasis on translational relevance to orthopaedic surgery and perioperative decision-making. Given the scoping nature of the review and the heterogeneity of available evidence, study selection focused on identifying representative and clinically informative literature rather than exhaustive quantitative inclusion. Discrepancies in study relevance were resolved by consensus.

ELIGIBILITY CRITERIA

Studies were eligible if they evaluated BPC-157, thymosin beta-4 or marketed derivatives (including TB-500), GHK-Cu, or other peptide-based agents commonly promoted for musculoskeletal healing or recovery and reported outcomes relevant to musculoskeletal pathology, orthopaedic surgery, postoperative recovery, or perioperative risk domains. Preclinical animal studies, in vitro mechanistic investigations, and human clinical studies were eligible. Human evidence included randomized trials, cohort studies, case-control studies, case series, and case reports. Studies focused exclusively on non-musculoskeletal indications without clear translational relevance were excluded. Non-English publications were excluded if full-text translation was not available.

DATA EXTRACTION

Extracted variables included study design, peptide agent and formulation, dosing regimen and route of administration when reported, musculoskeletal indication, comparator group, outcome measures, efficacy findings, and adverse events. Mechanistic endpoints were recorded when available, including markers of inflammation, angiogenic activity, collagen organization, and bone remodeling. Human clinical evidence was prioritized for synthesis, with preclinical evidence used to contextualize biologic plausibility. Data extraction and synthesis were performed iteratively, with emphasis on clinical relevance and perioperative applicability.

EVIDENCE SYNTHESIS

Given heterogeneity in models, dosing, and outcome reporting, findings were summarized using structured narrative synthesis rather than quantitative pooling. Evidence was grouped by peptide agent and clinical domain, including tendon and ligament healing, cartilage and osteoarthritis, bone remodeling and fracture repair, wound healing, and postoperative recovery. Perioperative implications were evaluated with emphasis on orthopaedic surgical risk domains relevant to total joint arthroplasty (TJA), including wound complications, hematoma formation, immune modulation, infection susceptibility, heterotopic ossification, and implant fixation considerations. Commonly encountered agents were summarized by proposed mechanism, evidence tier, and perioperative considerations (**Table 1**).

Table 1. Common Peptide Agents Encountered in Orthopaedic Patients

Agent	Commonly Marketed Indications	Proposed Mechanism(s)	Evidence Tier for Musculoskeletal Outcomes	Key Safety and Perioperative Concerns
BPC-157	Tendon and ligament healing, muscle recovery, cartilage repair, postoperative recovery	Angiogenesis signaling, inflammatory modulation, fibroblast migration, collagen remodeling, nitric oxide pathway effects	Predominantly preclinical; minimal human clinical evidence	Unverified formulation and sterility; unclear dosing and pharmacokinetics; unknown perioperative effects on wound biology, hematoma risk, and infection susceptibility
Thymosin beta-4	Soft-tissue healing, muscle recovery, wound healing	Cytoskeletal regulation, cell migration, angiogenesis, inflammatory signaling modulation	Predominantly preclinical; limited human musculoskeletal evidence	Lack of orthopaedic surgical trials; uncertain dosing equivalence across products; unclear immune effects
TB-500 (marketed thymosin beta-4 derivative)	Recovery enhancement, tendon healing, rapid return to sport	Marketed as thymosin beta-4 analog with pro-angiogenic and remodeling effects	Minimal verifiable clinical evidence	Product authenticity uncertain; potential mislabeling; sterility risk; absence of perioperative safety data
GHK-Cu (copper tripeptide)	Wound healing, connective tissue repair, collagen support	Extracellular matrix remodeling, collagen regulation, inflammatory pathway modulation	Mechanistic and dermatologic evidence; minimal orthopaedic clinical evidence	No data in operative orthopaedics or TJA; uncertain systemic effects with injectable use; product purity concerns
CJC-1295	Lean mass, recovery enhancement, performance optimization	Growth hormone axis stimulation via GHRH analog activity	Limited human endocrine literature; no meaningful orthopaedic surgical evidence	Glycemic effects, edema, physiologic instability; unclear perioperative safety in comorbid surgical patients
Ipamorelin	Recovery enhancement, performance optimization	Growth hormone secretagogue	Minimal orthopaedic evidence	Potential metabolic effects; uncertain interactions with diabetes optimization and enhanced recovery pathways
Sermorelin	Recovery enhancement, anti-aging claims	GHRH analog with growth hormone stimulation	Minimal orthopaedic evidence	Similar endocrine and metabolic concerns; limited perioperative safety data
IGF-1 analogs	Muscle growth, tissue repair claims	Anabolic and proliferative signaling	Mechanistic evidence; limited clinical relevance to orthopaedic outcomes	Systemic growth signaling concerns; unclear safety profile; product verification challenges
Collagen peptides	Joint pain relief, connective tissue support	Substrate supplementation for extracellular matrix synthesis	Moderate human evidence in OA; limited surgical evidence	Generally low-risk oral supplement; heterogeneous formulations; unclear perioperative benefit
Thymosin alpha-1	Immune modulation claims	Immunologic signaling modulation	Limited musculoskeletal evidence	Potential immune effects relevant to infection risk; minimal orthopaedic outcome data
NAD (adjacent non-peptide agent)	Recovery and longevity optimization	Cellular redox cofactor, mitochondrial metabolic signaling	Not peptide; minimal orthopaedic perioperative evidence	Commonly co-administered; unclear perioperative physiologic effects; confounds exposure history

RESULTS

SEARCH RESULTS AND STUDY CHARACTERISTICS

The search identified a broad and heterogeneous body of literature spanning multiple peptide agents and a wide range of non-orthopaedic indications. Following relevance-based screening, approximately 20 to 35 studies were included in the final narrative synthesis. Consistent with the intent of an evidence-mapping scoping review, studies were selected based on translational relevance to musculoskeletal tissue healing, orthopaedic care, and perioperative decision-making. The evidence base was dominated by preclinical animal and mechanistic investigations, while human clinical outcome data were limited and largely observational. Across included studies, substantial variability existed in peptide formulation, dosing strategy, route of administration, and outcome reporting, limiting comparability and precluding quantitative synthesis.

BPC-157

BPC-157 was the most frequently represented peptide agent in musculoskeletal research. Preclinical studies have described effects on tendon healing, ligament repair, muscle regeneration, and inflammatory modulation (Vasireddi et al. 2025; Rahman et al. 2026). Multiple experimental models reported improved collagen organization, enhanced tensile strength, and pro-angiogenic signaling following injury. However, these findings were derived from heterogeneous models with inconsistent dosing regimens and variable outcome definitions (Cerovecki et al. 2010; Staresinic et al. 2003; Barisic et al. 2022). Few investigations incorporated clinically relevant comparators, standardized rehabilitation conditions, or endpoints directly translatable to postoperative recovery. Human evidence remains sparse, and no high-quality trials were identified evaluating BPC-157 in orthopaedic surgical populations. The current evidence base therefore does not support conclusions regarding efficacy in postoperative recovery or complication reduction. The limited available human clinical evidence evaluating BPC-157 and related peptide therapies in musculoskeletal settings is summarized in **Table 2**.

THYMOSIN BETA-4 AND TB-500

Thymosin beta-4 has been investigated in a smaller but mechanistically consistent body of literature, with reported effects on angiogenesis, cell migration, cytoskeletal regulation, and inflammatory signaling (Gonzalez-Franquesa et al. 2021; Goldstein et al. 2012; Philp et al. 2004; Yarmola et al. 2007). These pathways have contributed to widespread marketing of TB-500 as a recovery-enhancing therapy (Gonzalez-Franquesa et al. 2021; Goldstein et al. 2012; Philp et al. 2004; Yarmola et al. 2007). However, evidence directly applicable to musculoskeletal clinical outcomes remains limited. Most available data are preclinical or derived from non-orthopaedic clinical contexts, and robust human orthopaedic trials were not identified. In addition, TB-500 represents a marketed formulation rather than a standardized pharmaceutical product, introducing uncertainty regarding composition, dosing equivalence, and biologic predictability (Rahman et al. 2026). As a result, translation to surgical recovery and perioperative decision-making remains unsupported by high-quality clinical evidence.

GHK-CU

GHK-Cu is marketed for wound healing and connective tissue repair and has been described in mechanistic and dermatologic literature suggesting potential effects on collagen synthesis and extracellular matrix remodeling (X. Wang et al. 2017; Pickart 2008). While these pathways are theoretically relevant to soft-tissue recovery, orthopaedic-specific evidence remains minimal. No studies were identified evaluating GHK-Cu exposure in patients undergoing TJA or other major orthopaedic procedures. Accordingly, any inference regarding clinical benefit or perioperative risk is speculative.

GROWTH HORMONE SECRETAGOGUES AND IGF-1 ANALOGS

Growth hormone secretagogues, including CJC-1295, ipamorelin, and sermorelin, and IGF-1 analogs are increasingly used in wellness and optimization settings and are frequently co-administered with BPC-157 or TB-500 (Rahman et al. 2026). These agents are mechanistically distinct from tissue-targeted peptides and may influence recovery physiology through systemic endocrine pathways (Clemmons et al. 2017; Falutz et al. 2010; Raun et al. 1998; Stanley et al. 2014; Beck et al. 2014; Teichman et al. 2006). However, orthopaedic-specific clinical evidence supporting improved healing or postoperative recovery is lacking. In contrast, potential perioperative relevance may relate to metabolic instability, including glycemic effects, fluid retention, and blood pressure variability, particularly in older or comorbid surgical populations. The absence of surgical outcome data limits risk quantification, but the systemic endocrine activity of these agents warrants heightened perioperative caution. Regulatory and governance considerations relevant to orthopaedic patients, including athletes, are summarized in **Table 3**.

PERIOPERATIVE AND ARTHROPLASTY-SPECIFIC IMPLICATIONS

Across all peptide categories, direct evidence evaluating perioperative outcomes was limited. No high-quality studies were identified assessing the impact of peptide exposure on wound complications, hematoma formation, infection rates, or implant outcomes following TJA. Nevertheless, pathways implicated in preclinical studies, including angiogenesis, inflammatory modulation, and collagen remodeling, intersect with biologic systems central to incision healing and complication avoidance, although these mechanistic signals have not been shown to translate into improved clinical outcomes. In TJA, where the consequences of wound failure and PJI are severe, the absence of validated safety data is clinically meaningful. Furthermore, sourcing

Table 2. Human Clinical Evidence Evaluating BPC-157 and Related Peptides in Musculoskeletal Conditions

Agent	Human Evidence Identified	Clinical Setting	Key Findings	Quality and Applicability
BPC-157	Limited retrospective clinical report	Knee pain treated with injection	Symptomatic improvement reported in a subset	Low quality; uncontrolled; unclear formulation verification; not generalizable to surgery or TJA
BPC-157	Phase I safety and pharmacokinetic trial registered	Healthy volunteers	Safety and pharmacokinetics only	Not orthopaedic; does not establish efficacy or perioperative safety
Thymosin beta-4 / TB-500	No robust orthopaedic surgical trials identified	Musculoskeletal recovery claims	No high-quality clinical outcomes	Evidence insufficient for clinical recommendations
GHK-Cu	No orthopaedic surgical trials identified	Wound-healing claims	No TJA-relevant outcomes	Evidence not applicable to orthopaedic perioperative decision-making
GH secretagogues / IGF-1	No musculoskeletal surgical trials identified	Performance medicine exposure	Endocrine effects described	Not studied for healing or postoperative outcomes

Table 3. Regulatory and Governance Status of Peptide Agents Relevant to Orthopaedic Patients

Category	Examples	Regulatory or Governance Status	Practical Orthopaedic Implication
FDA approval for musculoskeletal healing	BPC-157, TB-500	Not FDA-approved for orthopaedic indications	Use should be considered unvalidated; perioperative safety and dosing cannot be assumed
Compounding and bulk substance concern	BPC-157	Listed in FDA safety communications regarding compounding risk	Heightened concern regarding formulation variability and sterility
WADA prohibited substances	Many peptide-related performance agents	Restricted under WADA frameworks	Athletes may face sanctions; surgeons should counsel regarding disclosure and documentation
Professional sports and collegiate restrictions	NFL, NCAA, UFC and others	Listed as prohibited substances	Medicolegal and career implications for competitive athletes; relevant to preoperative counseling

introduces uncertainty in sterility and formulation integrity, which may represent a more immediate and clinically relevant risk than theoretical biologic effects, particularly given the potential for nonsterile preparation, contamination, or inconsistent formulation in nonregulated injectable products. Key perioperative risk domains relevant to TJA and implant-based surgery potentially affected by peptide exposure are summarized in **Table 4**.

DISCUSSION

INTERPRETATION OF THE CURRENT EVIDENCE

The central finding of this review is the imbalance between clinical uptake and clinical evidence. BPC-157 and thymosin beta-4 derivatives are increasingly used for musculoskeletal recovery, yet the available literature remains dominated by preclinical models with minimal human validation (Vasireddi et al. 2025; Mayfield et al. 2026; Rahman et al. 2026). Across multiple experimental settings, these agents demonstrate biologic activity involving angiogenesis, inflammatory modulation, fibroblast migration, and collagen remodeling. These signals support biologic plausibility and justify further translational investigation, but do not establish clinical benefit. However, mechanistic plausibility does not establish clinical benefit, and the current evidence base does not support claims of improved healing, accelerated recovery, or reduced complication rates following orthopaedic surgery.

SAFETY, PRODUCT INTEGRITY, AND THE PROBLEM OF UNREGULATED SUPPLY

The primary clinical concern is not simply uncertainty regarding biologic effects, but uncertainty regarding product composition, sterility, and manufacturing quality. Most peptide products used in real-world settings are obtained through nonregulated sources with unclear manufacturing standards, variable concentration, and uncertain sterility.

Table 4. Perioperative Risk Domains Relevant to Total Joint Arthroplasty Potentially Affected by Peptide Exposure

Risk Domain	Importance in TJA	Evidence Strength	Surgeon Takeaway
Wound healing and incision integrity	Primary determinant of early complications and PJI risk	Mechanistic plausibility only	No evidence supports benefit; perioperative continuation cannot be justified
Hematoma formation and persistent drainage	Strong risk amplifier for PJI	No clinical data	Hold unregulated injectables preoperatively to minimize modifiable uncertainty
Immune modulation and infection susceptibility	Central to PJI development	Indirect evidence only	Absence of safety data is clinically meaningful in elective implant surgery
Sterility and contamination exposure	Potential catastrophic consequence in arthroplasty	Clinically plausible	Product integrity may represent dominant perioperative risk
Osseointegration and implant fixation	Critical in cementless THA and TKA	No clinical evidence	No basis to recommend peptides for fixation enhancement
Heterotopic ossification	Function-limiting complication after THA	Theoretical	Unknown effect; no evidence supports use
Metabolic instability	Influences wound healing and infection risk	Indirect endocrine evidence	GH secretagogues and IGF-1 analogs warrant additional caution
Complication attribution and documentation	High medicolegal relevance in elective TJA	Not applicable	Document peptide exposure and counseling explicitly

Injectable administration further magnifies this risk by introducing the possibility of local tissue reaction, systemic inflammatory exposure, and contamination-related complications. This distinction is critical, as even a biologically promising compound may become clinically harmful when delivered through nonstandardized formulations. The absence of verified pharmacokinetics and product verification prevents evidence-based recommendations regarding discontinuation timing, perioperative safety, and postoperative resumption, leaving surgeons unable to quantify risk in elective operative settings. This is particularly relevant for injectable formulations obtained outside standard pharmaceutical channels, where risks of contamination, endotoxin exposure, or improper compounding may exceed any theoretical biologic effect. Many of these agents are not approved by the FDA for musculoskeletal indications and may be compounded or sourced outside regulated pharmaceutical manufacturing pathways.

IMPLICATIONS FOR TOTAL JOINT ARTHROPLASTY

TJA represents a uniquely high-stakes setting for peptide exposure. Even modest increases in hematoma formation, persistent drainage, or delayed wound healing may amplify susceptibility to PJI, a complication with disproportionate morbidity and resource utilization. Potential mechanisms by which peptide exposure could influence surgical outcomes include dysregulated angiogenesis contributing to hematoma formation, altered inflammatory signaling affecting early wound healing, and perturbations in collagen organization that may influence soft-tissue integrity during the critical postoperative period.

While direct evidence linking peptide use to PJI or implant failure is lacking, the absence of high-quality safety data should not be interpreted as reassurance. The combination of unverified formulation, uncertain sterility, and unknown systemic effects creates a perioperative exposure that cannot be reliably risk-stratified. In elective TJA, where tolerance for biologic uncertainty is low, the most defensible approach remains risk minimization. At the same time, if verified peptide formulations were ultimately shown to enhance soft-tissue recovery without increasing infection risk, the clinical relevance for TJA would be substantial, underscoring the importance of rigorous clinical investigation rather than informal adoption.

ADJACENT AGENTS AND REAL-WORLD STACKING BEHAVIOR

Patients using BPC-157 or TB-500 frequently engage in broader self-directed health or recovery strategies, often combining multiple agents with overlapping physiologic effects. GHK-Cu is marketed for wound healing and connective tissue remodeling, while endocrine-active compounds such as growth hormone secretagogues and IGF-1 analogs are used to augment recovery and performance (Pickart and Margolina 2018; Rahman et al. 2026). NAD, while not a peptide, is frequently administered in the same longevity settings and reflects the broader ecosystem of perioperative supplementation (Gallagher and Emmanuel 2026). This stacking behavior complicates medication reconciliation and increases uncertainty surrounding glycemic stability, fluid shifts, and inflammatory response. In practice, counseling is most effective when focused on defining the specific agent, route of administration, source reliability, and timing relative to surgery rather than debating unproven efficacy claims. It is important to distinguish orally administered supplements, such as collagen peptides, from in-

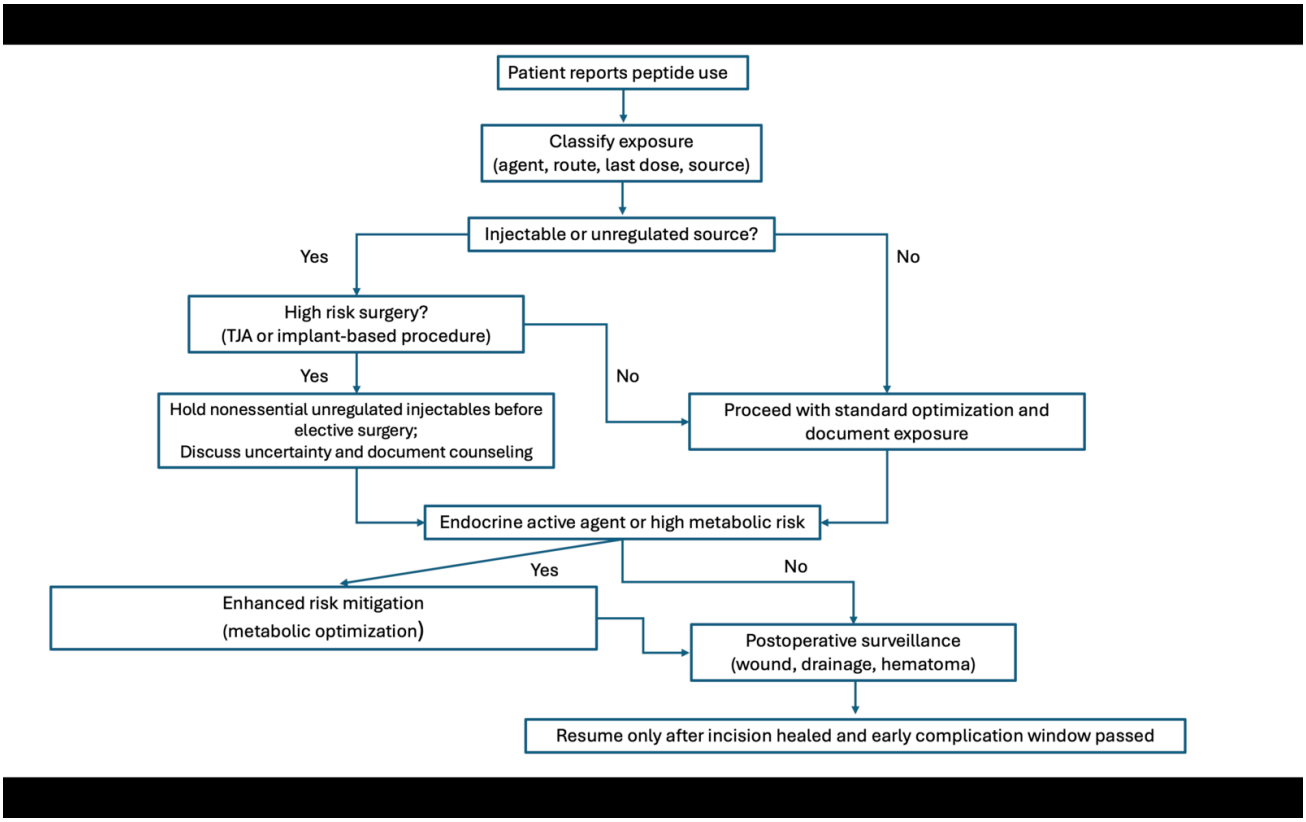


Figure 1. Proposed Perioperative Counseling and Risk-Minimization Algorithm for Patients Reporting Peptide Use

Clinical decision framework for perioperative management of patients reporting use of peptide therapies or related biologic optimization agents. The algorithm emphasizes exposure characterization, identification of injectable or formulations with uncertain sterility, stratification by surgical risk (including total joint arthroplasty and other implant-based procedures), and recognition of endocrine-active agents or metabolic comorbidity that may increase perioperative vulnerability. Given the absence of validated safety data and uncertain product integrity, a conservative approach is recommended, including discontinuation of nonessential unregulated injectable agents before elective surgery, heightened postoperative surveillance for wound-related complications, and delayed resumption until incision healing is complete and early complication risk has passed.

jectable biologics, as oral formulations generally have a different safety profile and do not introduce risks related to sterility or injection-related complications.

CLINICAL COUNSELING AND PERIOPERATIVE MANAGEMENT

In the absence of validated efficacy and perioperative safety data, surgeons require a pragmatic framework. Patients should be counseled that current evidence supporting peptides is largely preclinical, that human surgical outcomes are poorly studied, and that product purity and sterility cannot be assumed. For procedures in which complications are catastrophic, including TJA, counseling should prioritize discontinuation of nonessential injectable biologics before surgery, explicit documentation of exposure, and heightened vigilance for early wound complications. These discussions should remain neutral and evidence-driven, recognizing that many patients interpret peptide use as proactive health optimization. A transparent explanation of evidence limitations and surgical risk priorities is more likely to preserve trust and compliance than confrontational dismissal. A pragmatic perioperative counseling and risk-minimization framework is proposed for orthopaedic surgical patients reporting peptide exposure (**Figure 1**).

RESEARCH PRIORITIES AND THE TRANSLATIONAL OPPORTUNITY

Despite limited clinical evidence, the biologic plausibility and widespread exposure base represent a translational opportunity for orthopaedics. Future investigations must prioritize product verification, dose characterization, and adverse event surveillance before efficacy can be responsibly evaluated. Prospective studies should incorporate clinically meaningful endpoints rather than surrogate mechanistic outcomes. For sports procedures, these include validated functional scores, return-to-sport timing, and complication surveillance. For TJA, priority endpoints include wound complications, prolonged drainage, hematoma requiring intervention, early readmission, and PJI, with follow-up sufficient to capture early revision risk. Without standardized formulations and defined perioperative protocols, clinical trials will remain vulnerable to confounding and irreproducibility.

Importantly, the current evidence gap should not be interpreted as evidence of ineffectiveness. Many therapies now considered foundational in perioperative medicine were initially adopted based on mechanistic plausibility and early observational signals before high-quality surgical outcome trials were performed. If standardized peptide formulations can be verified and administered within con-

trolled protocols, these agents may represent a future adjunct to evidence-based perioperative care, particularly in populations undergoing TJA where wound healing, metabolic health, and inflammatory regulation strongly influence outcomes.

FUTURE DIRECTION AND CALL TO ACTION

The current evidence gap presents an opportunity for orthopaedic investigators to establish high-quality prospective registries evaluating peptide exposure in real-world musculoskeletal populations. Systematic capture of dosing patterns, formulation source, route of administration, and standardized clinical outcomes may be more informative than continued reliance on heterogeneous mechanistic studies. In particular, elective procedures with high consequence complications, including TJA, warrant carefully designed observational cohorts with validated patient-reported outcomes, wound surveillance, and adverse event monitoring. Such registries, coupled with independent product verification and transparent conflict-of-interest disclosure, represent a critical step toward determining whether clinically meaningful benefit exists and whether perioperative risk can be quantified. Rather than allowing peptide use to remain confined to nonmedical distribution channels, orthopedics should lead the development of standardized perioperative registries and prospective trials using verified formulations, with the goal of determining whether peptide-based therapies can be safely integrated into evidence-based surgical optimization.

LIMITATIONS

This review is limited by the structure of the existing literature. Most studies evaluating BPC-157, thymosin beta-4 derivatives, and related peptide agents are preclinical, employ heterogeneous dosing regimens, and report surrogate endpoints that do not translate directly to operative recovery or implant-based outcomes. Human musculoskeletal evidence is sparse and rarely includes verified product composition, standardized exposure assessment, or perioperative endpoints relevant to TJA. In addition, real-world use is frequently confounded by co-administration of multiple agents and inconsistent sourcing, limiting external validity and complicating attribution of benefit or harm. Accordingly, conclusions should be interpreted as an evidence map and perioperative risk framework rather than confirmation of clinical efficacy or safety.

CONCLUSIONS

Peptide therapies are increasingly used among musculoskeletal patients, yet high-quality evidence supporting clinical efficacy and perioperative safety remains limited. Preclinical studies demonstrate biologic activity relevant to tissue repair, supporting biologic plausibility but not clinical effectiveness. The current combination of uncertain benefit and uncertain product integrity warrants a cautious and structured clinical approach. In total joint arthroplasty, where wound complications and periprosthetic joint infection carry substantial consequences, perioperative risk minimization should remain the priority. Future investigation using verified formulations and prospective clinical study designs is necessary to determine whether peptide-based therapies can be safely and meaningfully integrated into orthopedic care.

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