Prolactin: A New Actor in Musculoskeletal Physiology and its Implication in Orthopedic Pathologies

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Abstract

Prolactin (PRL), traditionally known for its role in lactation, has emerged as a pleiotropic hormone with actions that extend beyond reproduction. Growing evidence suggests its involvement in pain modulation, immune function and tissue homeostasis, with potential repercussions on musculoskeletal health. This review analyzes in depth the available scientific literature on PRL and its relationship with orthopedic pathologies, including chronic pain, tendinopathies, and conditions of the muscle, ligaments, and articular cartilage. The molecular and cellular mechanisms underlying the influence of PRL on musculoskeletal physiology are explored, as well as the clinical implications of its level disturbances, both hyperprolactinemia and hypoprolactinemia. Finally, future perspectives and lines of research are discussed to fully understand the role of PRL in the context of orthopedic pathologies are discussed.

Keywords: Prolactin, Hyperprolactinemia, Hypoprolactinemia, Chronic pain, Tendinopathies, Osteoarthritis, Skeletal muscle, Ligaments, Articular cartilage, Prolactin receptors

Introduction

Prolactin (PRL), a polypeptide hormone produced mainly by lactotroph cells of the adenohypophysis, is mainly recognized for its role in lactogenesis [1]. However, PRL exerts a wide range of physiological actions that extend beyond reproduction, participating in more than 300 biological processes, including regulation of the immune system, metabolism, behavior, and tissue homeostasis [2].

In recent decades, research has revealed an emerging role for PRL in musculoskeletal physiology. In vitro and in vivo studies have shown that PRL influences the growth, differentiation, and function of various cell types, including muscle cells, chondrocytes, osteoblasts, and fibroblasts [3]. Furthermore, PRL participates in the modulation of the inflammatory response, angiogenesis, and pain perception.

This literature review focuses on the scientific evidence that links PRL with orthopedic pathologies, including chronic pain, tendinopathies, and conditions of the muscle, ligaments, and articular cartilage. The mechanisms by which alteration of PRL levels, both hyperprolactinemia and hypoprolactinemia, could contribute to the development and progression of these conditions are explored. Furthermore, the clinical implications of these findings are discussed, and future lines of research are suggested.

Production and Regulation of PRL

PRL is synthesized mainly in the lactotroph cells at the adenohypophysis, although it is also produced in other tissues such as the brain, decidua, mammary glands, and the immune system [4]. The regulation of PRL secretion is complex, and it involves an interaction between stimulatory and inhibitory factors.

Dopamine, produced in the hypothalamus, is the main inhibitor of PRL secretion, acting through dopamine D2 receptors in lactotroph cells [4,5]. In the other hand, stimulating factors include: Thyrotropin-releasing hormone (TRH), vasoactive intestinal peptide, estrogen, and nipple sucking [1]. Furthermore, PRL can self-regulate its secretion through a negative feedback mechanism, acting on PRL receptors (PRLR) in the hypothalamus [6].

Hyperprolactinemia

Hyperprolactinemia, defined as an increase in blood levels of PRL, can be caused by a variety of physiological and pathological factors.

Physiological causes

• Pregnancy: During pregnancy, PRL levels increase progressively, reaching their peak at the time of delivery. This increase is essential for the development of mammary glands and lactogenesis [7].

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Submitted Date: 10 May 2025, Review Date: 20 May 2025, Accepted Date: May 2025 & Published: 30 Jun 2025

Journal of Regenerative Science | Available on www.jrsonweb.com | DOI:10.13107/jrs.2025.v05.i01.161

• Breastfeeding: Nipple sucking during breastfeeding stimulates the secretion of PRL, maintaining milk production.
• Stress: Physical or emotional stress can cause a temporary increase in PRL levels [1].
• Sleep: PRL levels increase during sleep, especially during deep sleep phases [2].
• Physical exercise: Intense exercise can stimulate the secretion of PRL.
• Diet: Eating foods rich in protein can increase PRL levels [1].

Pathological causes
• Prolactinomas: Prolactinomas are benign tumors of the pituitary gland that secrete PRL in excess, being the most common cause of pathological hyperprolactinemia [3].
• Hypothyroidism: A deficiency of thyroid hormones can cause an increase in TRH, which in turn stimulates the secretion of PRL.
• Hypothalamic diseases: Lesions or tumors that affect the hypothalamus can interfere with the production of dopamine, disinhibiting the secretion of PRL.
• Polycystic ovary syndrome (PCOS): PCOS is associated with a mild increase in PRL levels in some women, although the exact cause of this association is unclear.
• Drugs: Certain medications, such as antidepressants, antipsychotics, antiemetics, and opiates, can block dopamine D2 receptors or stimulate TRH secretion, causing hyperprolactinemia [4,5].

Hypoprolactinemia
Hypoprolactinemia, defined as a decrease in blood levels of PRL, is less common than hyperprolactinemia. The main causes include:
• Sheehan syndrome: A postpartum pituitary necrosis caused by severe hemorrhage during childbirth. PRL deficiency can result in the inability to breastfeed.
• Radiotherapy or pituitary surgery: Radiotherapy or pituitary surgery can damage lactotroph cells, reducing PRL production [6].
• Dopaminergic drugs: Medications that stimulate dopamine D2 receptors, such as bromocriptine and cabergoline, are used to treat hyperprolactinemia, but may cause hypoprolactinemia as a side effect [7].

PRL Measurement and Normal Values
PRL is measured by blood testing, preferably in the morning, after fasting for at least 8 h and at rest. It is important to avoid physical or emotional stress before this test, as it can raise PRL levels. Normal ranges vary depending on age, sex, and physiological status [3].
• Non-pregnant women: 2–29 ng/mL
• Pregnant women: 10–209 ng/mL
• Postpartum women: 100–400 ng/mL
• Men: 2–18 ng/mL.
It is important to consider that reference ranges may vary slightly between laboratories.

Effect of Altered PRL Levels on Pain Perception
PRL participates in the modulation of pain perception through complex mechanisms that involve the interaction with neurotransmitters, neuropeptides and opioid receptors in the central and peripheral nervous system.
Altered PRL levels may stimulate pain through sensitization of nociceptors specifically in females. PRL acts on certain nociceptive receptors, intensifying the perception of pain and promoting pain-like behaviors in female animal models. This process may involve the modulation of ion channels, such as TRPV1, TRPA1, and TRPM8, which are related to pain sensation, resulting in an increased response to inflammatory pain or stress-related pain [8].

Hyperprolactinemia and pain
Studies in animals and humans suggest that hyperprolactinemia may increase pain sensitivity and contribute to the development of chronic pain. PRL has been observed to enhance the activity of nociceptive neurons at the spinal cord and facilitate the transmission of pain signals to the brain. In addition, PRL can induce the release of proinflammatory substances that sensitize nerve endings and contribute to hyperalgesia. It has also been reported that in humans, stress increases circulating PRL and reduces sensory thresholds, increasing the probability of pain attacks [9].

Hypoprolactinemia and pain
Although less studied, hypoprolactinemia could also influence pain perception. It has been observed that the administration of exogenous PRL can have analgesic effects in animal models of inflammatory and neuropathic pain. These findings suggest that PRL could have a protective role against pain and that its deficiency could contribute to pain hypersensitivity.

Effect of PRL Levels Disturbances on Pathologies of Muscle Tissue, Ligaments and Articular Cartilage
PRL exerts direct and indirect effects on muscle tissue, ligaments, and articular cartilage, modulating processes such as growth, differentiation, cellular function, extracellular matrix synthesis, and the inflammatory response [10].

Skeletal muscle
PRL can influence skeletal muscle function and growth through interaction with PRLR present in muscle cells [11]. Animal studies have shown that PRL promotes muscle hypertrophy and increases muscle strength. On the other hand, hyperprolactinemia has been associated with myopathy and muscle weakness in humans. The mechanisms underlying these effects are not completely elucidated but could involve modulation of the expression of genes related to muscle growth, protein synthesis, and energy metabolism [12].

Ligaments
PRL may influence ligament health by modulating the proliferation, differentiation, and function of fibroblasts, the cells responsible for the synthesis and maintenance of ligament connective tissue. In vitro studies have shown that PRL stimulates the production of collagen and other extracellular matrix proteins by ligament fibroblasts. Additionally, PRL can modulate the inflammatory response in ligaments, influencing healing and tissue remodeling after injury.

Articular cartilage
PRL may influence articular cartilage homeostasis by modulating the function of chondrocytes, the cells responsible for the synthesis and

maintenance of the cartilage extracellular matrix. In vitro studies have shown that PRL can stimulate proliferation and proteoglycan synthesis by chondrocytes. However, hyperprolactinemia has been associated with increased cartilage degradation and the development of osteoarthritis in animal models [13].

The underlying mechanisms of these effects could involve the modulation of the expression of matrix metalloproteinases (MMPs) and other cartilage-degrading enzymes.

Implications of PRL levels disturbances in tendon pathology

PRL can influence tendon biology by modulating the proliferation, differentiation, and function of tenocytes, the cells responsible for the synthesis, and maintenance of tendon connective tissue.

Hyperprolactinemia and tendinopathy

Animal studies suggest that hyperprolactinemia could contribute to the development of tendinopathies, characterized by pain, stiffness, and decreased tendon function. It has been observed that PRL can increase the expression of pro-inflammatory cytokines and MMPs in tendons, which could contribute to the degradation of the extracellular matrix and tendon dysfunction. In addition, PRL may affect tendon vascularization, compromising its ability to repair and regenerate.

Hypoprolactinemia and tendinopathy

Although more research is needed, hypoprolactinemia could also have implications for tendon health. It has been observed that PRL can stimulate the proliferation and migration of tenocytes, which could promote tendon repair after an injury. However, further studies are needed to fully understand the impact of hypoprolactinemia on tendon pathology.

Hyperprolactinemia and Hypoprolactinemia Symptoms

Hyperprolactinemia

Symptoms of hyperprolactinemia can vary depending on sex and the underlying cause. In women, hyperprolactinemia can manifest as:

- Menstrual disorders: Amenorrhea (absence of menstruation) (80–90%), oligomenorrhea (irregular menstruations) (70–80%) and anovulation (lack of ovulation) [7].
- Galactorrhea: Milk production outside of pregnancy or lactation (30–80%) [14].
- Infertility: Difficulty conceiving due to impaired ovulation and luteal function [3].
- Decreased libido: Loss of sexual desire associated with decreased estrogen levels.
- Hypoestrogenism related symptoms: Vaginal dryness, hot flashes, osteoporosis (in cases of prolonged amenorrhea) [15].
- Hirsutism: Excessive hair growth in male patterns (in some cases).
- Osteoporosis: hyperprolactinemia plays a role in stimulating bone resorption, while suppressing bone formation [16].

Hyperprolactinemia can manifest in men as follows:

- Erectile dysfunction: Difficulty in achieving or maintaining an erection due to decreased testosterone levels (60–70%) [17].
- Decreased libido: Loss of sexual desire.
- Infertility: Impairment of sperm production and semen quality.
- Gynecomastia: Development of breast tissue in men (in some cases).
- Osteoporosis: Bone weakening (in cases of prolonged hypogonadism)

In addition to the sex-specific symptoms, hyperprolactinemia can cause general symptoms such as:

- Headaches: PRL has been identified as a sensitizing factor for pain-related structures, also within the trigemino-vascular system, which has specific relevance to migraine [3,18].
- Visual disturbances: Vision problems, such as loss of peripheral vision, may occur if a prolactinoma compresses the optic nerve [7].
- Symptoms of hypogonadism: Fatigue, depression, mood changes, difficulty concentrating.

Hypoprolactinemia

The most common and characteristic symptom of hypoprolactinemia is the inability to lactate or insufficient breast milk production following childbirth. Other potential symptoms include:

- Infertility: This may occur in some cases, although it is less common than in hyperprolactinemia.
- Increased risk of osteoporosis: PRL may play a role in bone health, and its deficiency could increase the risk of osteoporosis.

Discussion

PRL, initially recognized for its crucial role in lactation, has been shown to be a hormone with pleiotropic functions that impact various physiological systems, including the musculoskeletal system. This review has explored the scientific evidence supporting the influence of PRL on the physiology of muscles, tendons, ligaments, and articular cartilage, as well as its potential involvement in the development of orthopedic pathologies such as chronic pain, tendinopathies, and osteoarthritis.

The studies reviewed reveal that PRL exerts its effects through interaction with PRLR, which are present in a variety of cells within the musculoskeletal system, including myocytes, tenocytes, chondrocytes, and fibroblasts. Binding of PRL to its receptor triggers intracellular signaling cascades that regulate fundamental processes such as proliferation, differentiation, apoptosis, extracellular matrix synthesis, and the production of inflammatory mediators.

Alteration of PRL levels, either due to excess (hyperprolactinemia) or deficiency (hypoprolactinemia), can disrupt the homeostasis of the musculoskeletal system and contribute to the development of pathological conditions. Hyperprolactinemia has been associated with increased pain sensitivity, degradation of articular cartilage, tendon dysfunction, and muscle weakness. In contrast, hypoprolactinemia could affect tendon repair and increase the risk of osteoporosis.

It is important to emphasize that PRL does not act in isolation within musculoskeletal physiology. Its interaction with other hormonal, inflammatory, and mechanical factors modulates its impact on tissue health. For example, PRL can interact with sex hormones such as estrogen and testosterone, influencing bone mineral density and muscle strength. Furthermore, PRL may modulate the inflammatory response in the context of musculoskeletal injuries, affecting healing and tissue regeneration.

The clinical implications of these findings are relevant for the diagnosis and management of patients with orthopedic pathologies.

Evaluating PRL levels could be useful in identifying individuals at risk of developing, or already presenting, conditions such as chronic pain, tendinopathies, or osteoarthritis. In particular, patients with symptoms suggestive of hyperprolactinemia, such as menstrual disturbances, galactorrhea, erectile dysfunction, or infertility, should be assessed to exclude the presence of a prolactinoma or other causes of hyperprolactinemia.

It is important to mention that during the performance of this review, we never had support from endocrinology specialists, alluding to the fact that it is not an important issue; however, we believe that from the specialty in orthopedic surgery, teamwork and a better understanding of hormonal pathologies are essential to provide a better quality of life to patients with chronic pain.

Recommendations and Future Lines of Research

In light of the evidence presented, the following recommendations are suggested:

- To incorporate the evaluation of PRL levels in the clinical evaluation of patients with chronic musculoskeletal pain, tendinopathy, or osteoarthritis, especially in those with symptoms suggestive of hyperprolactinemia or hypoprolactinemia.
- To consider treating hyperprolactinemia with dopamine agonists, such as bromocriptine or cabergoline, in patients with orthopedic pathologies that do not respond to conventional therapies.
- To investigate the efficacy and safety of exogenous PRL administration in patients with hypoprolactinemia and musculoskeletal conditions.
- To promote research on the role of PRL in the prevention of musculoskeletal injuries, especially in at-risk populations such as athletes and postmenopausal women.

Future lines of research should focus on:

- Elucidating the precise molecular and cellular mechanisms by which PRL influences musculoskeletal physiology.
- Determining the role of PRL in the pathogenesis of different types of chronic pain and tendinopathies.
- Evaluating the effectiveness of pharmacological and non-pharmacological treatments aimed at modulating PRL in patients with orthopedic pathologies.
- Developing biomarkers based on PRL for early diagnosis and monitoring of orthopedic pathologies.
- Investigating the interaction of PRL with other hormonal, inflammatory and mechanical factors in the context of musculoskeletal health.

Conclusion

PRL is a hormone with significant implications for musculoskeletal health. Alteration of its levels can contribute to the development of chronic pain, tendinopathies, and other orthopedic conditions. It is essential to continue investigating the role of PRL in this context to optimize the diagnosis and treatment of these conditions.

Declaration of patient consent: The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given the consent for his/ her images and other clinical information to be reported in the journal. The patient understands that his/ her names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Conflict of interest: Nil **Source of support:** None

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Conflict of Interest: NIL
Source of Support: NIL

How to Cite this Article

Terán Vela PG, Tobar EAL, Freire LEG | Prolactin: A New Actor in Musculoskeletal Physiology and its Implication in Orthopedic Pathologies | Journal of Regenerative Science | Jan-Jun 2025; 5(1): 14-18.