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PROLACTIN AS AN IMMUNOMODULATOR IN RHEUMATIC DISEASES: THE POTENTIAL ROLE OF PHYSICAL EXERCISE IN THE PROLACTIN-IMMUNE AXIS

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ABSTRACT

Background and Objectives. Prolactin (PRL) is produced by pituitary and extra-pituitary tissues and signals via the prolactin receptor (PRLR), a class I cytokine receptor that activates pathways such as JAK2/STAT5, supporting a cytokine-like role in immune regulation [1-3]. Exercise and heat stress can transiently increase PRL and may confound interpretation in rheumatology [4-6]. We review PRL/PRLR evidence across systemic autoimmune rheumatic diseases and discuss implications for PRL testing around physical activity.
Materials and Methods. Narrative review of PubMed/MEDLINE and PubMed Central (inception–15 February 2026) using terms related to PRL/PRLR, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), Sjögren's syndrome (pSS), exercise and heat stress. Evidence was synthesized qualitatively given heterogeneity in assays, sampling and outcomes. Macroprolactin and analytical interference were considered as key confounders [1, 7, 8].
Results. Associations between mildly elevated PRL and disease activity were most consistent in SLE, supported by observational studies and syntheses, while interventional data with dopamine agonists remain limited and heterogeneous [9-11]. Findings in RA and pSS were more variable, with stronger signals for local PRL/PRLR relevance than for serum PRL as a universal biomarker [12, 13]. Acute vigorous exercise and passive heat exposure can raise PRL, potentially mimicking disease-related hyperprolactinemia if sampling is not standardized [4, 5, 14, 15].
Conclusions. PRL is a plausible neuroendocrine-immune modulator in rheumatic disease, particularly SLE [11, 16, 17]. Exercise should not be restricted on PRL grounds, but PRL testing should be standardized relative to recent exertion and thermal stress [5, 14, 15, 18].

KEYWORDS

Prolactin, Immunomodulator, Rheumatic Diseases, Physical Activity, Endocrinology, Immunology

CITATION

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Introduction

Clinical problem: In routine rheumatology care, patients with systemic autoimmune disease may undergo prolactin (PRL) testing because of menstrual disturbances, infertility, galactorrhea, or incidental laboratory findings. A common scenario is a patient with systemic lupus erythematosus or inflammatory arthritis who is physically active and presents with a mild-moderate PRL elevation measured shortly after vigorous training, sauna or heat exposure, poor sleep or acute stress. The clinician must decide whether the result represents true hyperprolactinemia that warrants endocrine work-up, a pre-analytical confounder, or a signal potentially relevant to autoimmune activity. This review addresses this intersection between PRL biology, systemic rheumatic disease, and exercise physiology, with a focus on practical interpretation.

Systemic autoimmune rheumatic diseases are characterized by chronic immune activation, autoantibody production and fluctuating inflammation that intersect with neuroendocrine pathways. Prolactin (PRL), classically linked to lactation, is also produced extra-pituitarily and signals through the prolactin receptor (PRLR), a member of the class I cytokine receptor family, activating pathways such as JAK2/STAT5. These features support a cytokine-like role for PRL in immune regulation and autoimmunity [1, 2].

At the same time, exercise is recommended by professional societies for inflammatory arthritis and other rheumatic and musculoskeletal diseases because it improves function, pain and cardiometabolic risk. However, exercise is an acute neuroendocrine stressor that can transiently increase PRL, especially at higher intensity and with heat stress[4, 5, 14].

This creates a practical uncertainty: whether short-lived, exercise-induced PRL elevations could meaningfully influence autoimmune pathways or disease activity, or whether they are clinically negligible compared with the anti-inflammatory benefits of regular training. Therefore, this review aims to synthesize

current evidence on PRL physiology in autoimmunity and on PRL responses to exercise, and to discuss potential clinical implications for patients with systemic autoimmune rheumatic diseases. Overall, available data suggest that exercise remains beneficial and safe, while the clinical relevance of transient PRL fluctuations is likely context-dependent and insufficiently defined, warranting further targeted studies.

Materials And Methods

This is a narrative review. PubMed (including MEDLINE-indexed records) and PubMed Central were searched from inception to 15 February 2026 using combinations of terms related to:

(I) prolactin biology and measurement ("prolactin", "hyperprolactinemia", "macroprolactin", "prolactin receptor")

(II) rheumatic diseases ("systemic lupus erythematosus", "rheumatoid arthritis", "Sjögren's syndrome", "systemic sclerosis", "vasculitis")

(III) physical activity ("exercise", "training", "heat stress").

We included English-language, peer-reviewed human studies (systematic reviews, meta-analyses, randomized controlled trials, and observational studies). Mechanistic animal and in vitro studies were included only when they clarified biological plausibility relevant to rheumatology. Single-patient case reports were excluded unless they illustrated clinically actionable diagnostic pitfalls (e.g. macroprolactin-related misclassification of hyperprolactinemia)[3]. Due to heterogeneity in PRL assays, timing of sampling, and reported outcomes across studies, evidence was synthesized qualitatively.

Results

Key evidence and practical considerations are summarized in Tables 1-3.

1. Across experimental and translational literature, PRL is implicated in lymphocyte proliferation and survival, dendritic-cell maturation, cytokine modulation, and B-cell tolerance disruption in models of systemic autoimmunity [6]. Immune cells can express the prolactin receptor (PRLR) and may also produce PRL locally, supporting autocrine and paracrine signaling. Despite biological plausibility, clinical translation is limited because circulating PRL is pulsatile and influenced by multiple confounders, reducing its reliability as a standalone biomarker [2]. The overall conceptual framework is summarized in (Figure 1).

PRL is not only an endocrine hormone but also a pleiotropic immunomodulator produced locally by immune and stromal cells. Extra-pituitary PRL has been described in lymphocytes and inflamed tissues, supporting paracrine signaling that may not be captured by a single serum measurement. Mechanistically, PRL binds PRLR isoforms and activates JAK2/STAT5, MAPK, and PI3K pathways, which overlap with cytokine signaling and can influence activation thresholds in adaptive immunity [1, 3]. Clinical data suggest that the immunomodulatory profile of hyperprolactinemia may be **level-dependent**, with different chemokine patterns observed at moderate versus very high PRL concentrations [19].

Recent syntheses emphasize PRL's context-dependent ('paradoxical') role in immune regulation, acting as both a potential amplifier and modulator of inflammatory pathways depending on disease setting and host factors [20].

From a translational perspective, two issues are critical for rheumatology: (i) circulating PRL may reflect stress physiology rather than tissue bioactivity, and (ii) 'total PRL' assays can be confounded by macroprolactin, which is often biologically inactive but can spuriously elevate laboratory results. Therefore, any attempt to use PRL as a biomarker should specify assay platform, sampling conditions, and macroprolactin screening strategy[8, 21, 22].

2. Systemic lupus erythematosus

SLE has the most consistent clinical evidence linking PRL to disease activity. Observational studies and meta-analyses generally report higher circulating PRL in SLE than in controls, with variable correlations with activity indices such as SLEDAI[9, 16, 23]. Interventional evidence remains limited: small randomized and non-randomized studies of dopaminergic agonists (e.g. bromocriptine) suggest potential reductions in flare frequency or disease activity in selected populations, but findings are constrained by small sample sizes and heterogeneous background immunosuppression [12, 16]. Important confounders - including pregnancy, sleep disturbance, and stress - are often incompletely controlled, which may materially affect PRL measurements and observed associations [10].

Recent syntheses support an association between hyperprolactinemia and higher SLE activity scores, although between-study heterogeneity is substantial and confounding (stress, sleep, medications, thyroid disease) is frequently incompletely addressed [23, 24]. Importantly, the PRL signal may be

phenotype-dependent: postpartum flares, neuropsychiatric disease, and patients with persistent hyperprolactinemia may represent higher-yield subgroups for mechanistic and interventional work [16].

Therapeutically, dopamine agonists (e.g. bromocriptine or cabergoline) lower PRL via D2 receptor activation and have been tested in small SLE studies. A recent systematic review and meta-analysis suggests PRL reduction and possible clinical benefit, but trials are few, sample sizes are small, and outcomes are heterogeneous. Therefore, these agents should be considered investigational in routine rheumatology practice and ideally used within trial frameworks or after endocrinology consultation [11, 23].

In pediatric populations, cross-sectional studies in juvenile SLE also report higher PRL levels in more active disease, and correlations with activity indices have been described [17, 25]. Future studies should incorporate standardized activity indices, longitudinal sampling, and explicit assessment of macroprolactin and relevant endocrine comorbidities. (Table 1).

3. In RA, findings on basal serum PRL are heterogeneous, with some cohorts reporting higher PRL associated with disease activity and structural damage [1, 12]. More consistent evidence supports local relevance: PRLR is expressed in inflammatory synovial tissue, and synovial fluid studies suggest macrophage-derived PRL and links to macrophage activation, implying potential pathogenic contributions of local PRL/PRLR signaling even when serum PRL is within the reference range [10, 25, 26]. Neuroendocrine responsiveness may also be altered in active RA, complicating the interpretation of single serum measurements [27]. Recent single-cell and pathway-focused syntheses highlight the central role of synovial macrophage polarization and metabolic reprogramming in rheumatoid inflammation, providing a mechanistic context for interpreting neuroendocrine immune signals such as PRL [28].

While serum PRL results vary, several lines of evidence suggest that PRL/PRLR biology may be locally relevant in the synovium. PRLR expression has been demonstrated in synovial cells and infiltrating immune cells, and macrophage-derived PRL may contribute to local inflammatory circuits, potentially explaining discordance between tissue activity and circulating levels [29].

Clinical cohorts in early RA have explored associations of PRL with metabolic and inflammatory features, but effect sizes are modest and directionality is inconsistent. This supports interpreting PRL as a context-dependent marker rather than a universal disease-activity biomarker in RA [25].

Implication for review readers: in RA, PRL is best discussed as part of ‘neuroendocrine-immune crosstalk’ and tissue signaling, with explicit acknowledgement that routine PRL testing is not supported by current evidence unless clinically indicated by symptoms or medication effects (Table 1).

4. In primary Sjögren’s syndrome, subsets of patients demonstrate hyperprolactinemia or modestly higher mean PRL compared with controls, but correlations with autoantibodies or systemic manifestations are inconsistent [30]. Across other connective tissue diseases, available evidence is sparse and does not currently support PRL as a clinically actionable biomarker. PRL is best framed as a mechanistic hypothesis requiring further validation [2, 29].

In Sjögren’s syndrome and other connective tissue diseases, reported associations are less robust than in SLE. Reported hyperprolactinemia may reflect comorbid endocrine conditions, medication effects, or macroprolactin. Therefore, clinical interpretation requires careful phenotype and laboratory context rather than assuming disease-specific causality [13, 24].

Because PRL physiology intersects with reproductive and stress axes, special situations such as pregnancy, postpartum, and fertility work-ups warrant explicit consideration when PRL is discussed in autoimmune populations [31]. (Table 1).

5. Exercise physiology of prolactin

Acute exercise can transiently increase PRL, with responses influenced by intensity, duration, thermal load, hydration status, and training state [4, 5, 14, 32]. Heat stress and higher core temperature amplify PRL responses, and heat acclimation may modify PRL kinetics [6, 18, 33]. Exercise may also acutely upregulate PRLR expression on immune cells, providing a plausible route for short-term changes in PRL sensitivity [30]. Most data derive from healthy cohorts. In rheumatic disease, inflammation, medication use, fatigue, and sleep disturbance may alter baseline neuroendocrine function and PRL response profiles [22, 34]. (Table 3).

From a practical standpoint, transient PRL elevations are most relevant for study design and laboratory interpretation. For clinical or research sampling, a conservative approach is to obtain blood after ≥30 minutes seated rest, avoid sampling immediately after vigorous exercise or sauna or hot-water immersion, and document recent exertion, sleep disruption, and acute stressors that can influence pituitary output [6, 14, 15].

Exercise prescription in rheumatic disease should follow established society recommendations and be individualized by baseline fitness, comorbidity burden, and disease activity. For most patients,

moderate-intensity aerobic and resistance training is safe and beneficial, while high-intensity interval training can be considered in selected inflammatory arthritis populations with appropriate screening and supervision [35-38].

An operational recommendation for this review's topic is therefore 'do not avoid exercise because of PRL', but 'avoid misinterpreting PRL': schedule PRL testing on non-training days or at least several hours after strenuous sessions, and consider macroprolactin testing when PRL results are discordant with symptoms or clinical context [39].

Discussion

This review supports converging biological plausibility and association data implicating PRL in rheumatic disease immunopathology - most consistently in SLE - whereas evidence in RA and primary Sjögren's syndrome is more heterogeneous and may depend on local tissue biology and neuroendocrine adaptation [2, 25, 27, 40]. A central unresolved issue is causality: higher circulating PRL may reflect stress physiology and inflammatory burden rather than act as a primary driver, and residual confounding is substantial across most clinical datasets [2, 22].

Exercise introduces a clinically relevant intersection. International recommendations endorse regular physical activity for inflammatory arthritis and osteoarthritis, and evidence in SLE increasingly supports exercise as safe and beneficial, improving aerobic capacity, fatigue, and quality of life [2, 41]. Although vigorous exercise and heat stress can transiently increase PRL, current evidence does not justify avoiding exercise because of PRL-related concerns[5, 6, 14]. A recent review of stress-system endocrine responses to different exercise modalities highlights that pituitary and stress hormones show marked variability across intensity, duration, and environmental conditions, supporting the need for standardized pre-analytical conditions when interpreting PRL results in physically active individuals [42]. Instead, these findings primarily inform measurement (i.e. avoid PRL sampling soon after vigorous or heat-stress sessions) and highlight a research opportunity to integrate standardized PRL/PRLR endpoints into exercise studies, including assessment of potential short-term changes in PRL sensitivity via PRLR expression[22, 30].

PRACTICAL APPROACH TO PRL TESTING IN PATIENTS WITH RHEUMATIC DISEASE

From a clinician's perspective, the most frequent pitfall is interpreting a single mildly elevated PRL value as a disease-related signal, without accounting for preanalytical factors. Acute vigorous exercise, sexual activity, sleep deprivation, and passive heat exposure (e.g. sauna) can transiently increase PRL and may overlap with the range reported in systemic autoimmune rheumatic diseases[5, 6]. Therefore, when PRL is used as an adjunct biomarker or is measured incidentally in rheumatology practice, sampling should be planned rather than opportunistic.

A pragmatic sampling strategy is to collect PRL in the morning after 15–30 minutes of rest, ideally on a non-training day, and to document recent high-intensity exercise or heat exposure. If PRL is above the laboratory upper limit, the next step should be to exclude macroprolactinemia and assay interference before initiating imaging or dopamine agonist therapy [14, 22, 43]. Contemporary laboratory literature supports systematic approaches based on polyethylene glycol precipitation or alternative methods (e.g. ultrafiltration) and highlights clinically meaningful variability between assays and populations [14, 43, 44]. In parallel, clinicians should consider medications and endocrine comorbidities that are common in rheumatology (e.g. antidepressants, antipsychotics, hypothyroidism) and interpret PRL values together with symptoms (amenorrhea, galactorrhea, infertility) and gonadotropins. Endocrinology references recommend repeating abnormal values, confirming persistent elevation, and then tailoring further evaluation to the degree of hyperprolactinemia and clinical context[22]. Importantly, mild elevations in the setting of systemic inflammation should be interpreted cautiously. Current interventional evidence for dopaminergic agonists in SLE is limited despite recent meta-analytic synthesis [25].

Physical Activity Recommendations And Implications for PRL Interpretation

RJR explicitly values guideline-linked, practice-oriented conclusions. For patients with rheumatic and musculoskeletal diseases, contemporary EULAR-informed evidence syntheses support physical activity as beneficial for disease-specific outcomes and quality of life, including in SLE and systemic sclerosis [28, 45]. This matters for PRL interpretation because the very behavior we promote - regular exercise - can acutely alter PRL dynamics. Thus, the key message is not to discourage activity but to standardize timing of blood sampling and to avoid over-investigation of isolated post-exertional PRL elevations.

In Sjögren's syndrome and related sicca presentations, PRL-related biology is also discussed in the context of prolactin-inducible proteins and tear film biomarkers [46-48]. Although these studies do not imply that serum PRL should be routinely measured in pSS, they illustrate how PRL-axis molecules may appear in peripheral tissues and why tissue-level pathways may not correlate tightly with a single serum measurement.

Areas of Uncertainty and Future Directions

Key uncertainties remain:

(I) whether PRL is a driver of autoimmunity or a stress-response epiphenomenon,

(II) whether PRLR signaling in target tissues is more relevant than circulating PRL, and (III) which patient subgroups would benefit from endocrine-immune modulation. In the near term, studies that combine standardized sampling, macroprolactin testing, and longitudinal clinical outcomes are most likely to clarify clinical utility [25, 43, 44]. Additionally, clinicians should remember that PRL secretion is pulsatile and stress-responsive. Repeating a borderline result under controlled conditions is often more informative than a single measurement. Where available, reporting of monomeric PRL can help distinguish true hyperprolactinemia from laboratory artifact and may reduce unnecessary imaging[43, 49]. Future trials should prespecify sampling conditions and include patient-important outcomes to clarify whether PRL adds incremental value beyond standard disease activity indices [28, 45].

Conclusions

Prolactin (PRL) emerges as a biologically plausible link between the neuroendocrine and immune systems, with the most consistent clinical associations observed in systemic lupus erythematosus. In other rheumatic diseases, particularly rheumatoid arthritis, evidence suggests that PRL may exert predominantly local, tissue-level effects rather than serving as a reliable systemic biomarker.

Importantly, physical exercise - despite its ability to induce transient increases in circulating PRL - remains a cornerstone of non-pharmacological management in rheumatic diseases and should not be restricted on this basis. Instead, these physiological fluctuations highlight the need for careful interpretation of PRL measurements, particularly in physically active individuals.

Future research should focus on standardized PRL assessment (including macroprolactin screening), improved control of pre-analytical confounders, and longitudinal designs integrating both systemic and tissue-level PRL/PRLR activity. Such approaches are essential to determine whether PRL has true clinical utility as a biomarker or therapeutic target in rheumatic diseases.

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Figures

Figure 1. Conceptual model of the prolactin-immune-exercise interface in systemic autoimmunity. Exercise and heat stress can transiently increase circulating prolactin (PRL) and modulate immune pathways via prolactin receptor (PRLR) signaling in immune cells, potentially influencing disease activity in systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and primary Sjögren syndrome (pSS).

Figure 2. Practical clinical workflow for prolactin (PRL) testing in rheumatology patients. The algorithm emphasizes pre-analytical standardization (including avoidance of recent exercise and heat exposure), repeat testing for mild elevations, assessment for macroprolactin and assay artifacts when indicated, and timely endocrinology referral and pituitary MRI when persistent hyperprolactinemia or red flags are present.

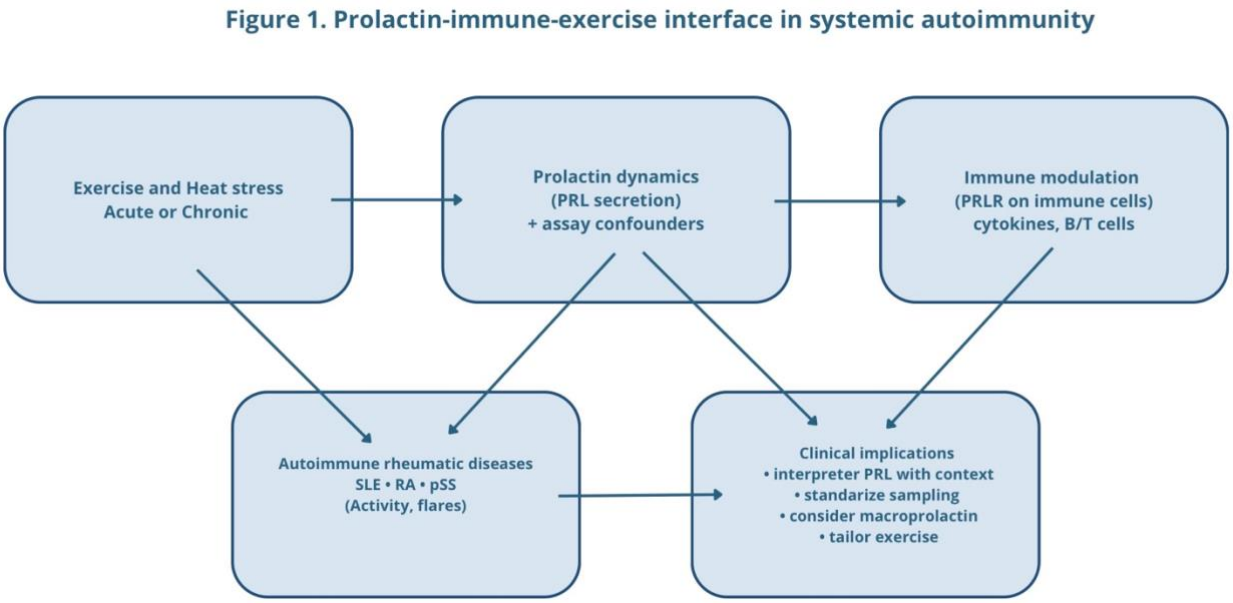
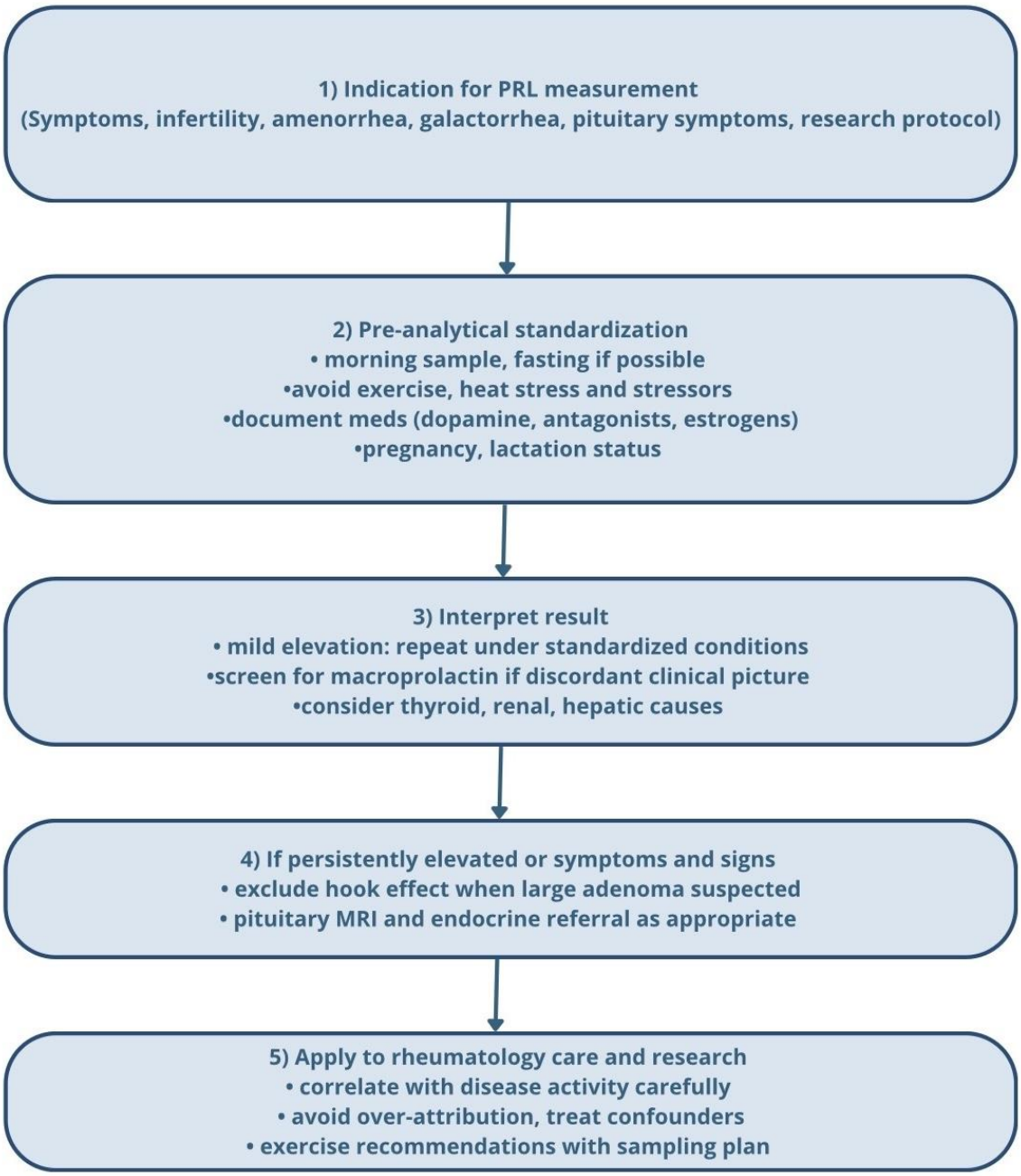


Figure 2. Clinical workflow for prolactin testing in rheumatology patients



Tables

Table 1. Summary of evidence linking prolactin to disease activity and pathobiology across selected rheumatic diseases.

Disease	Main PRL-related findings	Clinical relevance
Systemic lupus erythematosus (SLE)	Mild hyperprolactinaemia is more frequent than in controls, several cohorts and meta-analyses show higher PRL and correlation with activity indices (in subsets).	Consider endocrine confounders and assay issues, small RCTs or meta-analyses of dopaminergic agonists (e.g. bromocriptine, cabergoline) suggest possible activity reduction in selected patients[21, 24].
Rheumatoid arthritis (RA), Psoriatic arthritis (PsA)	Serum PRL-activity associations are inconsistent, synovial tissue shows PRLR expression and local PRL biology, suggesting a compartmentalized effect.	Supports a local PRL/PRLR axis, clinical utility of serum PRL as activity biomarker is limited [16].
Primary Sjögren's syndrome (pSS)	Data are limited, some reports link PRL to fatigue and autoantibodies but findings are heterogeneous.	Interpret cautiously, prioritize standardization (macroprolactin, medications, thyroid function) before attributing elevations to disease[22, 50].
Exercise, heat stress context (across diseases)	Acute high-intensity, prolonged exercise and heat stress can transiently increase PRL (dose- and environment-dependent).	Avoid PRL sampling shortly after strenuous exercise, heat exposure, document timing and conditions in clinics[11, 50].

Table 2. Key confounders and methodological considerations when interpreting prolactin measurements in rheumatology cohorts.

Domain	Key confounders	Practical recommendations (with citations)
Sampling physiology	Circadian rhythm, sleep, acute stress, pain, fasting status	Sample in the morning (e.g. 08:00-10:00) after ≥15-30 min rest, document acute stressors and recent sleep[22, 50].
Sex & reproduction	Menstrual phase, pregnancy and lactation, estrogen therapy, postpartum state	Record cycle day, contraception, interpret pregnancy, postpartum separately, avoid mixing reproductive states within analyses[22, 50].
Assay pitfalls	Macroprolactin, heterophile antibodies, high-dose hook effect, inter-assay variability	If PRL is elevated without typical symptoms, request macroprolactin (e.g. PEG precipitation) and consider repeat on an alternative assay, consider dilution if very high PRL[22].
Comorbidities	Primary hypothyroidism, renal, hepatic dysfunction, chest wall stimulation	Check TSH, free T4, assess renal, hepatic function when PRL is unexplained, address reversible causes first[22].
Medication	Antipsychotics, antidepressants, metoclopramide, domperidone, opiates, estrogens	Reconcile medication list, if feasible repeat PRL after drug changes (clinical judgment) and consult endocrinology when persistent[22].
Exercise, heat or stress exposure	Recent high-intensity training, endurance events, sauna, heat exposure, dehydration	Avoid sampling within 24 h of strenuous exercise, competitions and heat exposure, record ambient conditions and hydration[50].

Table 3. Exercise characteristics associated with higher prolactin responses and proposed clinical implications for rheumatology.

Exercise feature	Typical PRL response pattern	Implications for rheumatology research and clinical care (with citations)
High-intensity or prolonged endurance bouts	Transient PRL rise, amplified by heat stress, dehydration, returns toward baseline during recovery	Standardize intensity and environment, time blood draws (baseline, immediate post, 30-60 min), avoid conflating exercise-induced PRL surges with disease activity[11, 50].
Resistance exercise involving large muscle mass	Moderate PRL rise, interacts with stress response and inflammatory signaling	Collect perceived exertion and pain, avoid sampling during acute flares, document analgesic use[11].
Heat exposure	May augment PRL response, especially with dehydration	Avoid pre-visit heat exposure, record temperature, humidity and hydration strategies in trials[50].
Training status & habituation	Trained individuals may show attenuated endocrine responses at the same relative workload	Report training history, use relative intensity prescriptions (e.g. %VO2max/%1RM) to improve comparability [11].

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