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Review Article

Diagnosis of hyperprolactinemia by single serum prolactin determination: Challenges and recommendations

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Abstract

Secretion of prolactin follows a circadian rhythm of secretion, and several factors play an important role in the regulation of its secretion. An accurate diagnostic evaluation is essential for the proper management of the patient, which can be accomplished through a narrow observation and critical analysis of all the prolactin results which are above the standard upper limit of normal. If the circulating prolactin level exceeds five times the upper normal limit, a single test is sufficient to diagnose hyperprolactinemia. However, mildly elevated (20–40 ng/ml) results should be confirmed with at least two tests to counteract the circadian fluctuation or other factors causing transitory elevation. Repeat analysis of circulating prolactin on a later date preferably with 2–3 samples collected at few min interval is also recommended to minimize the effect of pulsatility when the elevation of serum PRL is doubtful (may be due to venipuncture induced stress) or when results are inconsistent with the clinical features. This review article presents an overview of the biological and analytical aspects of prolactin along with the impact of stress on prolactin secretion, as well as the current approach employed to tackle the chances of misdiagnosis and overtreatment. However, to understand the exact mechanism of stress induced hyperprolactinemia and its implications, further research is required.

Keywords: Prolactin, Hyperprolactinemia, Macroprolactin, Stress, Venipuncture, Variation

Introduction

Prolactin (PRL) was first introduced by Riddle *et al.* in 1933, and its role in proliferation and differentiation of the mammary cells as well as lactation was identified [1,2]. This review focuses on the biological and analytical aspects of this fascinating hormone along with the probable causes of variations in the analytical findings with special emphasis on stress induced variations, which are of interest to clinicians treating their patients.

Prolactin chemistry

Human PRL is encoded by a single gene on chromosome 6 [1,3,4]. It is a 23-kDa single-chain polypeptide of 198 amino acid residues and shares similar genetic and structural properties with growth hormone and placental lactogen [4,5].

Isoforms

Circulatory PRL has three molecular isoforms based on its size heterogeneity. In addition to its monomeric form, two other forms also exist, namely, a dimeric form 'big prolactin' of 50–60 k Da size and a larger polymeric form 'big-big prolactin' (macroprolactin) of greater than 150 k Da size, which is formed by binding 23 k Da prolactin with IgG autoantibodies. Both these forms exhibit minimal biological activity [1,4,6-11].

Secretion

PRL is secreted from the acidophilic lactotroph cells of the anterior pituitary gland, and several factors influence the regulation of PRL secretion. It follows circadian rhythm of secretion, with a nocturnal increase, showing 2–3 times higher secretion during the night. Maximum secretion occurs

during rapid eye movement (REM) sleep, and secretion is 20–30% higher in the morning than in the afternoon, reaching its peak between 4 AM and 6 AM. Short-term 'pulses' are less consistent [4,5]. Although no marked changes are observed during the menstrual cycle, there may be estrogen-induced slight mid-cycle elevation as estrogens have a direct action on the pituitary that increases PRL secretion [5,12]. There may be ectopic secretion of PRL from ovarian desmoids or bronchogenic carcinoma [7,13].

Regulation of prolactin secretion

Several factors play an important role in the regulation of PRL secretion. It is primarily under the inhibitory control of dopamine, wherein the secretion is suppressed through pituitary dopamine type 2 (D2) receptors [4,5]. Factors that have been identified to inhibit actions of dopamine neurons and thus indirectly upsurge PRL secretion include cholecystokinin, γ amino butyric acid (GABA), galanin, histamine, nitric oxide, noradrenaline, estrogen, opioids, and serotonin [1,5,14]. On the contrary, several factors, such as acetylcholine, angiotensin II, atrial natriuretic peptide, bombesin like peptides, calcitonin, neuropeptide Y, neurotensin, oxytocin, pituitary adenylate cyclase-activating peptide, thyrotropin releasing hormone, vasoactive intestinal peptide, and vasopressin inhibit PRL release (**Figure 1**) by stimulating dopamine neurons [1,15]. PRL secretion is also regulated through a short-loop negative feedback mechanism by PRL itself, increasing dopamine secretion and suppressing PRL secretion [1,16]. In addition, some cytokines are also involved in PRL secretion; for example, interleukin-1 (IL-1), IL-2, and IL-6 stimulate PRL secretion, whereas interferon gamma (INF-γ) and endothelin-3 are inhibitory cytokines [4,17]. Drugs, such as phenothiazines, increase PRL secretion [5]. Major stress such as that associated with general anesthesia and major surgery raises PRL secretion by several-folds. By contrast, there is no evidence that can objectively clarify whether minor stress, such as psychological trauma, outpatient attendance, and venipuncture, raises PRL levels [5,18]. Some physiological factors, including pregnancy and sucking, stimulate PRL secretion.

Metabolism

The biological half-life of PRL is 20–50 min. It is metabolized in the liver and eliminated by both liver and kidney. The normal adult circulating prolactin levels in case of female and males are 10–25 µg/L (10–25 ng/mL) and 10–20 µg/L (10–20 ng/mL), respectively [4].

Function

In addition to its key role in breast development and induction, as well as maintenance of lactation, PRL has several other functions. It inhibits secretion of gonadotropins through suppression of gonadotropin releasing hormone (GnRH) and thus impedes reproductive function [4]. It also plays an important role in water and electrolyte balance, immunoregulation [4,19,20], hepatocyte turnover [4,21], proliferation of vascular smooth muscle and intestinal mucosa [4,22,23]; it stimulates adipogenesis, inhibits lipolysis, and promotes insulin sensitivity [4,24].

Hyperprolactinemia (HyperPRL)

HyperPRL is an expression of an abnormal biochemical state rather than a medical condition. It implies to elevation of serum PRL levels above the standard upper limit of normal, presenting reproductive problems, mostly infertility in female. Prevalence of hyperPRL is 0.4%, affecting approximately 10 per 100,000 male and 30 per 100,000 females [4,5,7,9,25-29]. However, the estimated prevalence has been reported to be 5% in family planning clinic population and 17% in women with reproductive disorders [1,14]. The incidence is four times more in female aged 25–34 years than in males [4,25,26].

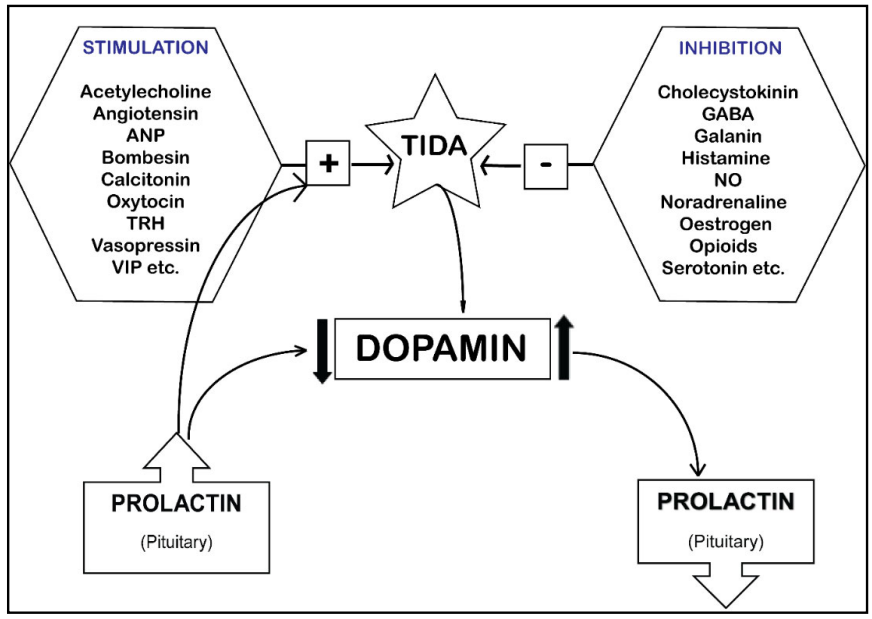

Figure 1. Regulation of prolactin secretion through dopamine and short loop feedback mechanism. TIDA: Tuberoinfundibular Dopaminergic Neurons; ANP: Atrial Natriuretic Peptide; GABA: γ Amino Butyric Acid; NO: Nitric Oxide; TRH: Thyrotropin Releasing Hormone; VIP: Vasoactive Intestinal Polypeptide.

HyperPRL may be functional, physiological, analytical, pathological, idiopathic, or pharmacological.

Functional/physiologic hyperPRL

Common physiological causes of hyperPRL are pregnancy and lactation. It may also increase following ingestion of high-protein diets, stress (including venipuncture), sleep, physical exertion, hypoglycemia, or sexual intercourse [1,7,30].

Analytical hyperPRL

Analytical causes of hyperPRL are also very common, and the presence of circulating big-big PRL or macroprolactin (MacroPRL) is the most likely cause. Approximately 4% of the general population are diagnosed with circulating MacroPRL, which presents a prevalence of 12.5–40% in patients with raised PRL results [1,7,31-33]. As MacroPRL is biologically inactive, it does not produce any clinical symptoms of hyperPRL and has no clinical significance. However, it may lead to misdiagnosis and imprudent treatment [7,34,35]. Sometimes macroPRL may also co-exist with hyperPRL. MacroPRL reportedly increases with advancing age, and it responds to dopamine antagonists and other physiological stimuli in a manner similar to monomeric PRL [6,7].

Pathological hyperPRL

The most alarming cause of pathological hyperPRL is sellar and parasellar lesions, including PRL secreting adenomas (prolactinoma, growth hormone/prolactin-secreting, adrenocorticotropic hormone/prolactin-secreting adenoma), hypothalamic/pituitary stalk disorders (granuloma, radiation, injury), non-pituitary tumours, sarcoidosis, craniopharyngioma, empty sella syndrome, vascular malformations and pituitary metastases [1,7,36]. HyperPRL may also be associated with primary hypothyroidism caused by thyrotroph and/or lactotroph hyperplasia, polycystic ovary syndrome, hepatic cirrhosis, epilepsy, chest injury, pseudopregnancy, Cushing's disease, and Addison's disease. Furthermore, hyperPRL is observed in chronic renal failure owing to decreased renal clearance [1,7,37-40].

Prolactinoma is the most common organic cause of hyperPRL and represents approximately 50% of the cases, showing a prevalence of 100 per 1 million [1,7,41-43]. It is more common in women and is usually benign; however, it may be malignant in some rare cases [7,44,45].

Idiopathic hyperPRL

Idiopathic hyperPRL is considered when no cause of hyperPRL can be identified and no visible pituitary adenomas are sighted on imaging. Typically, idiopathic hyperPRL presents a small microadenoma (<2 mm) which is too small for detection by imaging. Familial cases are also reported, caused by genetic mutation in PRL receptor located on chromosome 5, resulting in formation of inactive PRL isoforms and PRL insensitivity [1,7,46-49].

Pharmacological hyperPRL

HyperPRL associated with the use of various medications (listed in **Table 1)** has been reported to increase serum PRL by ten-fold above the baseline [1,7,9,50-53].

Diagnostic Strategies

For diagnostic evaluation, a thorough medical history, including symptoms, medications, comorbidities, excessive breast stimulation, and lifestyle factors, along with physical examinations for galactorrhea, gynecomastia, goiter, spider angiomas, ascites, facial edema, chest wall lesions, nipple piercings, and visual field defects are crucial. Further, hormonal assays and imaging studies can aid in the diagnostic evaluation of hyperPRL [1,9,27]. Estimation of circulating TSH, free T4, creatinine, IGF-1 levels, and β-hCG is recommended along with the measurement of serum PRL level to rule out secondary causes of hyperPRL [9,27,28,39,54-56]. After exclusion of all other probabilities of hyperPRL, magnetic resonance imaging or computerised tomography is indicated to detect any lesion compatible with pituitary tumour [9,56,57].

Table 1. List of pharmacological agents with the ability to induce hyperprolactinemia.

Sl. No.	Classes of Drugs	Examples
1	**Antipsychotics (neuroleptics)** A. First generation antipsychotics B. Second generation antipsychotics	 Chlorpromazine, Fluphenazine, Haloperidol Paliperidone, Risperidone, Quetiapine, Amisulpride
2	**Antidepressants** A. Tricyclic antidepressants B. Mono amine oxidase inhibitors C. Selective serotonin reuptake inhibitors D. Serotonin, noradrenaline reuptake inhibitors	 Amitriptyline, Desipramine, Clomipramine, Amoxapine Pargyline, Clorgyline Sertraline, Fluoxetine, Paroxetine Venlafaxine, Duloxetine, Reboxetine
3	**Other Psychotropics**	Buspirone, Alprazolam
4	**Antihypertensives**	Methyldopa, Verapamil, Reserpine
5	**Opioid analgesics**	Morphine, Methadone
6	**H_2 antagonists**	Cimetidine, Ranitidine
7	**Estrogens**	Oral contraceptives
8	**Prokinetics**	Amoxapine, Metoclopramide, Domperidone
9	**Others**	Fenfluramine, Physostigmine, Chemotherapies

Prolactin assays

Ideally, the best time of sample collection for blood testing is 2–3 h after waking [4]. Current methodology used to measure circulating PRL level is based on the two-site immunometric or sandwich assay principle, wherein the PRL present in the sample reacts with an immobilized capture antibody followed by a labelled detection antibody. The signal generated by the PRL-antibody complex is directly proportional to the amount of PRL present in the sample. Cross-reactivity or interference arising from circulating growth hormone, human placental lactogen, and heterophilic antibodies is rarely encountered with these types of sandwich assays [1,7,58].

PRL assay pitfalls

The contemporary automated immunoassay systems employing the sandwich assay principle are unable to differentiate between macroPRL and monomeric PRL. Therefore, along with the monomeric PRL, macroPRL can also bind with the capture and labelled antibody, which are used for the measurement of PRL and generate a high intensity signal for PRL, giving an erroneous result [6,7]. Such type of erroneous findings can be prevented by treating the serum with equal volume of 25% (w/v) polyethylene glycol (PEG) before processing the sample in immunoassay to precipitate the macroPRL. Although the gold standard for the diagnosis of macroPRL is gel filtration chromatography, PEG precipitation of serum is preferred as gel filtration chromatography is expensive and time-consuming [9,11,28,46,59-62]. PEG helps to precipitate immunoglobulin and immunoglobulin complexes and precipitates the macroPRL that contains IgG. However, it is observed that approximately 20% of the monomeric PRL is also co-precipitated with IgG [1,7,46,63].

Another common pitfall of the PRL assay is the hook effect. This is usually encountered when a significantly high circulating PRL saturates the antibodies employed in the two-site immunometric method. Consequently, labelled detection antibodies bind directly with the excess PRL without capture antibodies, thus giving erroneous results, which are lesser than the actual values [7,64]. This can happen in giant prolactinomas where the actual PRL levels can be several folds higher than the standard upper limit of normal but usually reported as normal [7,65]. This type of incongruity can be prevented by diluting the sera and serial dilution up to 1:100 [7,27].

In addition, high circulating biotin can also affect the PRL result by preventing formation of an antigen-antibody complex, thus yielding a deceptively low PRL result. Similarly, heterophilic or human anti-mouse antibodies may also interfere with PRL readings in patients with autoimmune diseases receiving antibody treatment [7,66,67]. In such cases, antibody precipitation, use of antibody blocking tubes, serial dilution of the sample, or the application of a different methodology for processing the sample may help to obtain a more accurate result [7].

Circulating PRL in Response to Stress

The biological response to stress is a very complex phenomenon, which causes secretion of adrenaline and noradrenaline, as well as the release of PRL. There is ample evidence supporting the role of PRL in numerous stresses induced systemic disease pathology, developed secondary to hyperPRL [4,68-71]. Therefore, it is of paramount importance to determine the mechanism by which PRL regulates and responds to emotional stress.

Mechanisms of stress-induced hyperPRL

As reported earlier, dopamine is not responsible for stress induced hyperPRL; PRL-realeasing-factors such as prolactin-releasing peptide (PrRP) are considered to be responsible for stress induced hyperPRL. Studies have shown that PrRP in animal models can stimulate corticotrophin-releasing hormone (CRH), mediate the release of adrenocorticotropic hormone (ACTH), and alter the hypothalamic-pituitary-adrenal (HPA) axis in conjunction with noradrenaline. It has also been reported that irrespective of the gender bias, a highly significant correlation exists between the magnitude of PRL secretion and magnitude of ACTH secretion in response to stress as both hormones are secreted from the anterior pituitary under the influence of same releasing factor [72]. Further, the nocturnal rise of PRL secretion is considered to be mediated by serotonin, which is presented as a multifaceted response to stress. However, it is too early to comment on the above observation as it requires further investigation and is therefore beyond the scope of this review [4].

Biological significance of stress-induced hyperPRL

The biological significance of stress induced hyperPRL is still under experimentation. There is evidence indicating the regulative role of PRL in response to stress. Experiments on animal models have revealed that PRL results in corticosterone release through its action on the adrenal gland [72,73]. It was also reported that the HPA axis reactivity could be inhibited by intra-cerebral infusion of PRL in animal model and thus could be considered as a regulator of stress response. Moreover, the level of the PRL release is correlated with the magnitude of the HPA-axis responses, though the mechanism is not fully understood. Prolactin has been reported to play a protective role against the damage caused by stress. It has been reported that stress induced hyperPRL acts as a buffer towards the immunosuppressive effects of stress and thus plays the role of an immune enhancing hormone. Reports also state that stress induced hyperPRL can prevent the development of gastric ulcer secondary to stress response [72].

The discrepancy of PRL responses in laboratory stress studies

Several studies have revealed that serum PRL level is elevated in response to acute psychological stress [72,74-77]. However, some studies have revealed completely contradictory results [72,78-83]. Several justifications related to these contradictory outcomes have been noticed. One narration is that the reduced or unaltered serum PRL level in response to acute stress may be attributed to the study design, wherein the baseline level of PRL is increased before the stress test owing to anticipatory stress, which masks the actual variation during the test [72,80]. Secretion of PRL follows a diurnal rhythm, and a nocturnal elevation is observed followed by a continuous and abrupt decline for few hours after awakening. If sampling is performed within this period, this functional decrease may have a significant influence on the stress test, which explains the unaltered or decreased status of PRL following the stress test [72,83].

Recommendation/Approach

HyperPRL is diagnosed when circulating PRL level reaches beyond 25 ng/mL (25 µg/L). However, in case of mildly elevated (20–40 ng/ml (20–40 µg/L) circulating PRL levels, diagnosis should be confirmed with at least two tests to counteract the circadian fluctuation or other factors causing transitory elevation. If the

circulating PRL level exceeds five times the upper normal limit, a single test is sufficient to diagnose hyperPRL [4,25]. Regarding ideal practice of sample collection for estimating circulating PRL, various recommendations and controversies have been reported [84,85]. According to the Endocrine Society Clinical Practice Guideline, a single measurement of circulating PRL is sufficient to confirm the diagnosis of hyperPRL provided sample collection is conducted without excessive venipuncture stress. Therefore, the probability of venipuncture induced stress mediated variation of circulating PRL cannot be ruled out and must be taken care of to minimize over diagnosis and treatment. Repeat analysis of circulating PRL on a later date preferably with 2–3 samples collected at an interval of 15–20 min is also recommended to minimize the effect of pulsatility when the elevation of serum PRL is doubtful (may be due to venipuncture induced stress) or when results are inconsistent with the clinical features [27,86,87]. It is also suggested that the elevated circulating PRL level must be re-evaluated before reporting unless it is clearly elevated (>80–100 ng/mL) [28,84,88]. Several studies have observed significant increase in the circulating PRL because of venipuncture induced stress and suggested serial sampling for analysis intervals of few minutes with a rest period [4,84,89-94]. In order to reduce pain and fear of multiple venipuncture pricks, it was also advocated to use intravenous catheter or cannula for sample collection [84,91,94]. However, preparing a pool from the samples collected at different time intervals with rest, followed by measurement of the analyte from the pooled sample was considered a better option as it could conserve time and resources [84,93,95,96].

Further, in case of asymptomatic hyperPRL, it is advisable to rule out macroPRL as macroPRL is a common cause of hyperPRL. Therefore, exclusion of macroPRL in all cases of hyperPRL or otherwise routine screening for macroPRL may help to exterminate unnecessary testing and treatment. In addition, the possibility of hook effect must be considered in regard to normal or moderate elevation of circulating PRL with a clinical presentation of large pituitary adenomas. The confirmation should be accomplished with dilution of the sample to prevent misdiagnosis and treatment [27,56,97,98].

Future Directions

The mechanism of action, as well as the regulation of secretion of PRL, is a very complex phenomenon. HyperPRL is regarded as a serious endocrine disorder; however, it is considered to be a natural and favorable condition during pregnancy and lactation. Experimental findings on animal models have revealed that stress exhibits a biphasic effect on circulating PRL levels, that is, an early brief phase of stimulation followed by an extended period of inhibition [99,100]. It was also evident that sudden exposure to stress resulted in an upsurge of circulating PRL. In contrast, repeated exposure to the same stressor failed to display any change in the serum PRL level. It appears that exposure to the same stressor causes adaptation to the stimulus, resulting in a lower physiological response [99,101]. Similar biphasic or "two faces" nature of PRL has also been observed in the immune system. At physiological concentrations, PRL stimulates NK cell activity, whereas at higher concentrations, it inhibits the NK cells [99,102]. PRL influences many physiological processes and plays a crucial role in various diseases. However, its mechanisms of action are not clearly understood and are the subject of research. Moreover, the role of PRL in metabolic homeostasis, immune regulation, and sex-dependent stress response also needs further elucidation [4,20].

Conclusive Remarks

Secretion of PRL is not only influenced by numerous environmental factors but is also strongly regulated by stress. Because of the significant role of this hormone in stress responses, it is often called the stress hormone. This review aims to present an overview of the biological and analytical aspects of PRL and the impact of stress on the PRL secretion as well as the current approach employed to address the chances of misdiagnosis and overtreatment.

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