The crucial role of prolactin-lactogenic hormone in Covid-19

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Abstract

Prolactin (PRL) is a peptide hormone secreted from anterior pituitary involved in milk production in the females and regulation of sex drive in both sexes. PRL has pro-inflammatory and anti-inflammatory functions. High PRL serum level or hyperprolactinemia is associated with different viral infections. In coronavirus disease 2019 (Covid-19), which caused by positive-sense single-strand RNA virus known as severe acute respiratory distress syndrome coronavirus type 2 (SARS-CoV-2), PRL serum level is increased. PRL in Covid-19 may exacerbate the underlying inflammatory status by induction release of pro-inflammatory cytokines. However, PRL through its anti-inflammatory effects may reduce the hyperinflammatory status in Covid-19. The underlying mechanism of increasing PRL in Covid-19 is poorly understood. Therefore, in this review we try to find the potential anti-inflammatory or pro-inflammatory role of PRL in Covid-19. As well, this review was aimed to discuss the underlying causes and mechanisms for Covid-19-induced hyperprolactinemia.

Keywords Prolactin · Covid-19 · Anti-inflammatory effects · Pro-inflammatory cytokines

Background

Prolactin (PRL) also known as lactotropin (lactogenic hormone with immune function) is a peptide hormone secreted from anterior pituitary involved in milk production in the females and regulation of sex drive in both sexes [1]. PRL is the only hormone secreted from anterior pituitary not activated by hypothalamic-releasing factor but under control of inhibitory effect of dopamine from the hypothalamus

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[2]. Dopamine inhibits release of PRL via dopamine receptor type 2 (D2) and deficiency of this receptor contributes into development of hyperprolactinemia [3]. PRL secretion is stimulated by suckling, thyrotropin-releasing hormone (TRH), estrogen, and vasoactive intestinal polypeptide (Fig. 1), [4]. Therefore, D2 agonists like bromocriptine and cabergoline inhibit PRL secretion, while D2 antagonists like sulpiride, risperidone, haloperidol, metoclopramide, and domperidone stimulate PRL secretion [5].

There are three circulating forms of PRL, which are little-PRL (22 kDa), Big-PRL (48 kDa), and Big-big PRL (150 kDa). Little-PRL or free PRL is the most active one, while Big-big PRL or macro-PRL has very low biological activity and appears to be predominantly circulated in postmenopausal women [6]. PRL acts through specific PRL receptors (PRLRs) belonging to the cytokine receptors super-family, which are also receptors for leptin, erythropoietin, colony-stimulating factor, and interleukin-6 (IL-6) [7].

PRLRs can also act as function receptors for growth hormone and placental lactogen [8]. As well, PRL may act as a cytokine-like action via activation of cytokine receptors in the regulation of immune system [9].

Therefore, the diverse function of PRL is related to activation of PRLRs and cytokine receptors through endocrine, paracrine, and autocrine manners (Fig. 2).
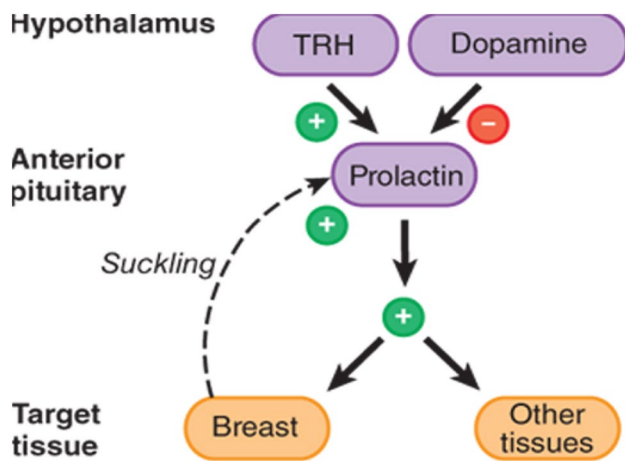
Fig. 1 Regulation of prolactin secretion: Thyrotropin-releasing hormone (TRH) stimulates prolactin secretion, while dopamine inhibits prolactin secretion
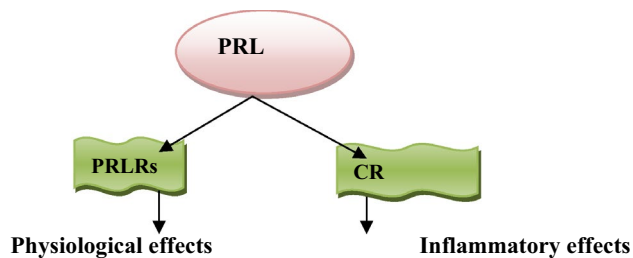

Fig. 2 Effects of prolactin (PRL): PRL activates PRL receptors (PRLRs) leading to the physiological effects. PRL activates cytokine receptors (CR) leading to inflammatory reactions

Moreover, PRL may be classified as a gonadotropin because it has luteotropic and weak gonadotropin effects. PRL inhibits secretion of gonadotropin-releasing hormone by unidentified mechanism, although PRLRs have been recognized in the hypothalamus [10].

Similarly, PRL suppresses secretions of testosterone in men and estrogen in women; however, physiological level of PRL improves Leydig cells function and stimulates testosterone secretion [11, 12].

Furthermore, PRL has pleiotropic effects, including improvement formation of myelin sheath of neuronal axons of central nervous system (CNS), fetal neurogenesis, promoting formation of lung surfactant, and immunological tolerance during pregnancy [13].

Extra-pituitary PRL is released from decidua, breast, myometrium, prostate, leukocytes, and lymphocytes that secretion is not affected by dopamine but by superdistal promoters. Extra-pituitary PRL (ePRL) has mainly autocrine and paracrine effects rather than endocrine effects

due to different bioactivity and molecular weight from pituitary PRL [14].

PRL serum level is high during sleep and early morning, it can be increased by exercise, emotional stress, high-protein diet, and following epileptic seizure [15]. Therefore, PRL serum level can be used to distinguish epileptic seizure, which associated with high PRL serum level from psychogenic seizure which associated with normal PRL serum level [16].

Pathologically, PRL serum level is elevated in various clinical conditions, such as prolactinoma, primary hypothyroidism, and adrenal failure. Hyperprolactinemia is defined when fasting PRL serum level more than 25 ng/mL in females and 20 ng/mL in males [17].

PRLRs are broadly expressed in different endocrine and target tissues as well as immune cells, including lymphocytes, monocytes, macrophages, granulocytes, microglia, natural killer (NK) cells, and thymic epithelial cells for controlling of immune response and reactions in autoimmune disorders [18].

There are various isoforms of PRLRs, which are large (PRLR-L), intermediate (PRLR-I), and small (PRLR-S) according to the size of intracellular domain, as the extracellular domains of PRLRs are identical.

Besides, soluble form of PRLR has been identified, but its precise function is not elucidated [18]. Therefore, PRL may act as an immune–endocrine link between the immune cells and endocrine disorders.

The coronavirus disease 2019 (Covid-19), which is caused by positive-sense single-strand RNA virus known as severe acute respiratory distress syndrome coronavirus type 2 (SARS-CoV-2), leads to acute tissue injury and exaggerated immune response [19]. Covid-19 patients are chiefly asymptomatic or presented with mild respiratory symptoms, although 5–15% of patients may develop pulmonary and extra-pulmonary complications [20]. Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) are the most common pulmonary complications [21].

Besides, extra-pulmonary complications like acute cardiac injury, acute brain injury, testicular injury, and different endocrinopathies could be the presenting symptoms [22, 23]. The diverse effects of SARS-CoV-2 infection is due to wide distribution of angiotensin-converting enzyme 2 (ACE2), which acts as receptor and entry point for this virus [24].

It has been reported that PRL has pro-inflammatory and anti-inflammatory functions [25]; therefore, the aim of the present study is to review the potential role of PRL in Covid-19.

Immunological role of prolactin

Activation of PRLRs may stimulate various inflammatory signaling pathways including mitogen-activated protein kinase (MAPK), extra-cellular signal regulated kinase 1/2 (ERK1/2), Janus kinase 2 (JAK2), signal transducer and activator of transcription 5 (STAT5), phosphoinositide 3-kinase (PI3K), and protein kinase B (PKB) resulting in pro-inflammatory or anti-inflammatory actions depending on the different isoforms of activated PRLRs [26]. In addition, PRL secretion is stimulated by IL-1, 1L-2, and IL-6 during active phase of chronic inflammatory disorders. Williams et al. observed that activation of macrophages by PRL through STAT3 result in release of anti-inflammatory cytokine IL-10 [27]. However, activation of macrophages by PRL through JAK2/STAT1 pathway results in release of pro-inflammatory cytokines, including tumor necrosis factor alpha (TNF-α), IL-1β, IL-12, and interferon gamma (INF-γ) [28].

Similarly, PRL provokes T cells activation via STAT5 signaling pathway leading to expression of T-box transcription factor (TBXF) [29]. Indeed, experimental study demonstrated that psychological stress-induced PRL secretion result in the induction of intestinal inflammation via alteration function of dendritic and T cells [29]. Further molecular studies revealed that PRL can activate expression of inducible nitric oxide synthase (iNOS) in the peripheral mononuclear cells via STAT5 signaling pathway and interferon regulatory factor 1 (IRF-1) [30]. Likewise, experimental study illustrated that expression of ePRL in the macrophages and monocytes are activated by adrenergic pathways with subsequent polarization of macrophages toward the inflammatory one (M1) [31].

Furthermore, PRL has important effects on the adaptive and innate immune responses; it increases expression of IL-2 on the lymphocytes and thymocytes with maturation of CD4+ and CD8+ [32].

A direct association between PRL serum level and CD4+ T lymphocytes has been clarified by induction expression of NF-κB and IRF-1 [33]. Likewise, high PRL serum level and hyperprolactinemia promote auto-reactivity by inhibiting B cells clonal deletion and alteration activation threshold and tolerance for B cells [34]. Indeed, PRL activates dendritic cells (DCs) for antigen presentation and production of INF-α [25].

As well, PRL promotes maturation and development of immune cells expressing major histocompatibility complex II (MHC-II) and co-stimulatory molecules, such as CD86 and CD40 [35].

Therefore, hyperprolactinemia is correlated with high level of auto-antibodies, like anti-pituitary and anti-cardiolipin auto-antibodies [36].

During pregnancy there is an immunological-tolerant state with adaptation due to shifting of immune response from the pro-inflammatory Th1/Th17 toward the anti-inflammatory Th2 immune response with development of regulatory T cells (Treg) [37].

It has been shown that PRL and estrogen have immunostimulatory effects, while progesterone and testosterone have immunoinhibitory effects during pregnancy [38].

Thus, high PRL serum level during pregnancy and lactation may provoke immunological disorders and development of autoimmune diseases, including systemic lupus erythematosus (SLE), peripartum cardiomyopathy, and rheumatoid arthritis [39]. Taken together, PRL has dual inflammatory and anti-inflammatory effects depending on the underlying pathophysiological conditions (Fig. 3).

Inflammatory role of prolactin

PRL through PRLRs, which distributed in various immune cells, can induce release of pro-inflammatory cytokines. PRL activates release of macrophage inflammatory protein-1α (MIP-1α), interferon protein 10(IP-10), chemokines, and monocyte chemoattractant protein 1 (MCP-1) from activated macrophages [28].

Similarly, PRL triggers macrophage cytotoxicity with generation of ROS, as well it induces expression of IRF-1 and iNOS in the granulocytes [40]. PRL also stimulates natural killer (NK) cells to produce INF-γ with activation survival of T cells and increase percentage of CD4 through inhibition of T cells apoptosis and production of pro-inflammatory cytokines that act as a co-stimulatory molecule promoting T cells survival [41]. In addition, PRL inhibits function of regulatory T cells (Treg) [42].

Alternatively, PRL activates antibody production by stimulating B cells through increment of intracellular calcium,
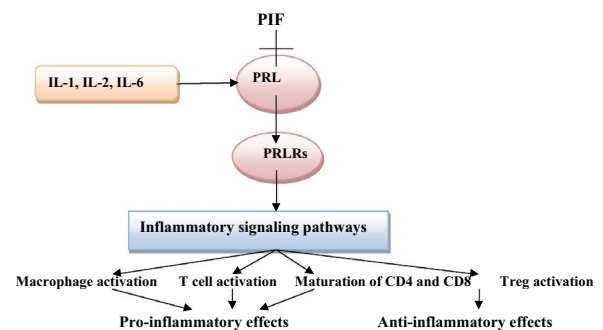

Fig. 3 Immunological role of prolactin (PRL): PRL is inhibited by PRL inhibiting factor (PIF) and stimulated by interleukins (ILs). PRL stimulates PRL receptors (PRLRs) causing activation of inflammatory signaling pathways with subsequent inflammatory or anti-inflammatory effects

suppression of B cells energy and inhibition expression of pro-apoptotic gene [42]. Thus, persistent elevation of PRL alters B cells function and promoting auto-reactivity.

Therefore, PRL through activation of T and B cells with stimulation of monocyte–macrophage axis promotes the cellular and humoral immune response with induction of inflammatory changes (Fig. 4).

So, PRL has important inflammatory role that induces and exaggerates different inflammatory disorders [32].

On the other hand, PRL has an anti-inflammatory against different autoimmune diseases, and recent evidences illustrated that PRL does not play a critical role in the development and progression of multiple sclerosis, experimental autoimmune encephalomyelitis, systemic lupus erythematosus, and even in experimental rheumatoid arthritis (RA) [43].

However, there is significant controversy regarding the role the anti-inflammatory and inflammatory role of PRL in RA, since systemic and locally produced PRL have different roles in RA [44]. The anti-inflammatory effects of PRL are documented in different experimental and clinical studies.

Olmos-Ortiz et al. illustrated that PRL reduces the immune response to the effects of lipopolysaccharide (LPS)-induced inflammation by attenuating expression toll-like receptor 4 (TLR4) and nuclear factor kappa B cells (NF-κB) with subsequent reduction release of pro-inflammatory cytokines, including TNF-α, IL-1β, and IL-6 [45].

Besides, PRL inhibits expression of TNF-α and IL-1β in human fetal membrane inflammation induced by LPS [46]. Interestingly, PRL increases circulating immunosuppressive progesterone by inhibiting 20-hydroxysteroid dehydrogenase that supports the anti-inflammatory effect of placental PRL (Fig. 5), [46].

Therefore, PRL have both pro-inflammatory and anti-inflammatory roles according to certain conditions, and these dual effects are greatly influenced by molecular compositions of the target cells during inflammatory milieu.

Role of prolactin in viral infection

It has been reported that high PRL serum level or hyperprolactinemia is linked with human immune deficiency (HIV) infection. Hyperprolactinemia in HIV infection is not related to the metabolic disorders, liver disturbance, viral load, and use of antiretroviral treatment [47]. A prospective study involved 192 men patients with HIV infection illustrated that hyperprolactinemia is observed in 21.4% of HIV-infected men patients and associated with higher CD4+ counts [47].

Besides, hyperprolactinemia could be a potential cause of hypogonadism in HIV-infected patients through inhibitory effect of PRL on the release of gonadotropin-releasing factor from the hypothalamus [48]. Although, a cohort study comprising 188 HIV-infected patients showed that
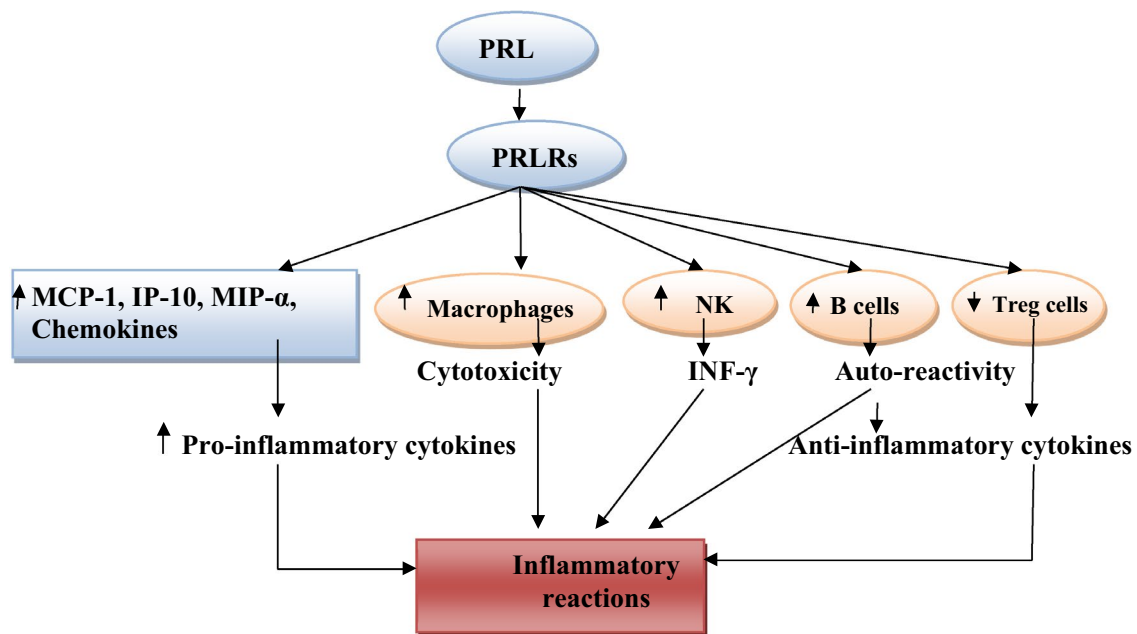

Fig. 4 Pro-inflammatory role of prolactin (PRL): PRL through PRL receptors (PRLRs) activates release of macrophage inflammatory protein-1α (MIP-1α), interferon protein 10(IP-10), chemokines, and monocyte chemoattractant protein 1(MCP-1). PRL also stimulates natural killer (NK) cells to produce INF-γ, PRL inhibits function of regulatory T cells (Treg), and PRL alters B cells function and promotes auto-reactivity and antibody production with subsequent inflammatory reactions
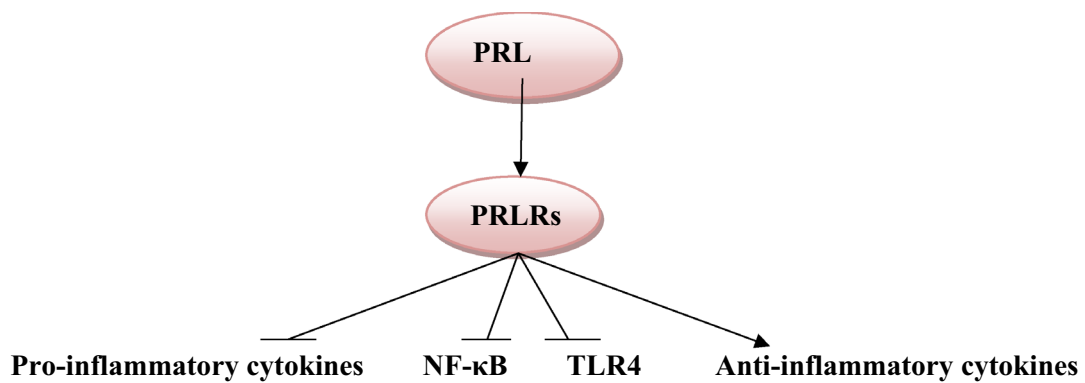
Fig. 5 Anti-inflammatory role of prolactin (PRL): PRL inhibits expression of pro-inflammatory cytokines, nuclear factor kappa B (NF-κB), and toll-like receptor 4 (TLR4) with activation of anti-inflammatory cytokines

hyperprolactinemia-induced hypogonadism in HIV is not related significantly to the inhibition of gonadotropin release [48].

Indeed, hyperprolactinemia is associated with hepatitis C virus infection (HCV), although this association is not linked with the extra-hepatic manifestation of HCV infection, like autoimmunity [49].

Kong et al. in vitro study demonstrated that PRL regulatory element binding (PREB) is regarded as a novel cofactor for HCV infection [50]. PREB is induced by HCV and promotes replication of HCV RNA through formation of HCV replication compartment [50].

These findings give a new insight into the role of PRL in HCV infection.

A prospective study illustrated that high PRL serum level is observed in HCV-infected patients compared to the healthy controls due to induction of PRL mRNA in the peripheral blood mononuclear cells by HCV [51]. Glal et al. observational study showed that high PRL serum level is linked with development of thrombocytopenia in patients with HCV infection as there was a negative correlation between PRL serum level and platelet counts [52].

High PRL serum level in HCV infection may cause immune-mediated thrombocytopenia through induction production of auto-antibodies by interfering with B cells tolerance with induction release of pro-inflammatory cytokines [53].

Furthermore, human cytomegalovirus (HCMV) infection induces expression of PRLRs by stimulating inflammatory signaling pathways including NF-κB and MAPK in ovarian cancer [54]. Both HCMV and PRL may share the same immunological pathway by activating inflammatory pathway and suppression of anti-inflammatory pathway that further improve virus replication and aggravate inflammatory reactions [54].

Accordingly, Wallis in 2021 demonstrated that CMV and other viruses like rubella can use PRLRs as receptor and entry point for viral–host cell interactions [55]. In SARS epidemic 2003, SARS-CoV led to significant increase in PRL serum level due to dysregulation of adenohypophyseal control by direct cytopathic effect or associated pro-inflammatory changes [56].

Moreover, a prospective cohort study involved 32 hospitalized infants with respiratory syncytial virus infection (RSV), which illustrated that severe infection of RSV is linked with high PRL serum level and lymphopenia [57].

Taken together, PRL serum level is augmented in different viral infections due to involvement of PRL in the pathogenesis of viral entry and replication and stimulation of PRL release by the associated activation of inflammatory signaling pathways. However, high PRL serum level in viral infections could be a compensatory mechanism due to the anti-inflammatory of PRL.

Prolactin and Covid-19

In Covid-19, there are noteworthy immunological and inflammatory changes that affect neuroendocrine homeostasis mainly in older patients with underlying co-morbidities. In addition, Covid-19-induced stressful status may affect release of PRL and other stress-mediated hormones [58].

It has been reported that PRL plays an important role in the regulation of immune function during viral infections, and hypoprolactinemia can cause death from opportunistic infections in patients with HIV infection [59]. Therefore, enhancement of PRL serum level toward the physiological values by dopamine antagonists may improve the immunological profile and survival in various critical statuses [60].

Petrulli et al. illustrated that systemic inflammation triggers activation of striatal dopamine with subsequent reduction in the release of PRL [61].

Hence, Sen proposed that dopamine antagonists could improve and boost the immune function in Covid-19

through augmentation release of immune-stimulant PRL [62]. Also, high PRL serum level in pregnant women, children, and cigarette smokers could be a protective factor against Covid-19 [62].

Interestingly, there is a significant controversy regarding PRL serum level in pregnant women, children, and cigarette smokers that might be normal, reduced, or elevated in these conditions [63].

It has been shown that hypothalamic TRH is regarded as a potent stimulator for PRL secretion from anterior pituitary [4]. In this sense, a prospective observational clinical trial in Italy involved 31 male attending care for infertility during Covid-19 lockdown which illustrated that TSH was significantly reduced by unidentified mechanism [64]. Low TSH serum level may trigger release of TRH from the hypothalamus with subsequent activation release of PRL from anterior pituitary in Covid-19. Similarly, a prospective study comprised 41 men patients with Covid-19 to assess the semen quality, which revealed that PRL serum level was elevated in those patients and remains elevated after recovery [65].

These findings suggest that SARS-CoV-2 infection can impair hypothalamic–pituitary–gonadal axis and by this mechanism may increase secretion of PRL from anterior pituitary in Covid-19.

In Covid-19, there are momentous interaction and cross-talk between hypothalamic–pituitary–adrenal (HPA) axis and SARS-CoV-2 infection, since pro-inflammatory cytokines and stress activate HPA, which also regulate response to the inflammatory cytokines [66].

A cohort, prospective study involved 28 Covid-19 patients which illustrated that cortisol and ACTH serum levels were reduced significantly in SARS-CoV-2 infection indicating impairment of adrenocortical response due to central adrenal insufficiency [66].

Of note, PRL serum level is increased in patients with adrenal insufficiency and in experimental studies [17, 67]. Kumar et al. cross-sectional study involved 235 Covid-19 patients, 21(8.5%) of them had hyperprolactinemia without sex difference, and this condition was not correlated with Covid-19 severity and mortality [68]. Besides, 25.1% of Covid-19 patients had primary hypothyroidism [68], which is similar to sick euthyroid syndrome reported in viral infections [69].

In addition, Schwaz et al. retrospective study comprised 54 Covid-19 patients which revealed that low free T3 serum level was correlated with risk of mechanical ventilation [70].

These findings suggest that hyperprolactinemia in Covid-19 may be stress induced as there were no relationship and correlation between PRL serum level and Covid-19 severity in absence of other endocrinopathies. However, secondary hyperprolactinemia in Covid-19 with primary hypothyroidism or adrenal insufficiency is linked with Covid-19 severity.

Previously, a cohort study showed that PRL serum level is increased in patients with septic shock-induced ALI [71] since; PRL has a crucial role in damping and regulation of immune response and inflammatory reactions. However, experimental study demonstrated that repeated administration of domperidone, a dopamine antagonist in experimental mice, leads to induction of ALI by exacerbating inflammatory-induced injury in lung epithelial cells [72].

It has been shown that calcitonin gene-related peptide (CGRP) has anti-inflammatory and broncho-protective effects, as well as vasodilator effects and tissue repair [73]. Ochoa-Callejero and colleagues exemplified that CGRP serum level is reduced in Covid-19 due to immune deregulation [74]. Likewise, deficiency of CGRP provokes development of autoimmunity through PRL upregulation and deficiency of anti-inflammatory cytokines [75]. Therefore, high PRL serum level in Covid-19 might be due to reduction of CGRP activity.

Of note, PRL has inflammatory or anti-inflammatory actions depending on the underlying pathological conditions. The anti-inflammatory role of PRL in Covid-19 could be beneficial in Covid-19 by mitigation exaggerated immune response. Paucity and limitation of published study regarding experimental and clinical trial studies concerning role of PRL in Covid-19 made this difficult and hard to prove the anti-inflammatory role of PRL in Covid-19. Of interest PRL has anti-inflammatory effects by attenuating expression TLR4 and NF-κB with succeeding decrease in the release of pro-inflammatory cytokines [45].

Fascinatingly, the anti-inflammatory role of PRL could be by increasing immunosuppressive progesterone [46]. In Covid-19, expression TLR4 and NF-κB are activated and augmented leading induction release of pro-inflammatory cytokines with development of ALI, ARDS, and cytokine with MOFs [76].

Pinna in 2020 suggested that sex steroids including progesterone hormone have anti-inflammatory and immune regulatory effects that protect women from Covid-19 and could have a potential role against Covid-19 in postmenopausal women and men [77].

In addition, Devi et al. experimental study illustrated that PRL inhibits expression of MAPK in the ovary with development of premature ovarian failure [78].

Thus, PRL may inhibit MAPK-mediated endothelial dysfunction and immunothrombosis in Covid-19 [79]. Therefore, high PRL serum level in Covid-19 might be a compensatory mechanism against activated TLR4/NF-κB/MAPK axis and low progesterone in Covid-19.

On the other hand, PRL is regarded as pro-inflammatory agent increased release of pro-inflammatory cytokines and development of immunoinflammatory disorders.

Notably, PRL activates release of macrophage inflammatory protein-1α (MIP-1α), interferon protein 10(IP-10),

chemokines, and MCP-1 from activated macrophages [28]. PRL increases macrophage cytotoxicity with generation of ROS [40]. PRL stimulates NK cells to produce INF-γ with activation of T cells and production of pro-inflammatory cytokines [41]. Furthermore, PRL inhibits function of (Treg) cell [42].

Also, PRL activates antibody production by stimulating B by prompting B cell auto-reactivity [42]. Therefore, inflammatory signaling pathways play important role in immune dysregulation during Covid-19.

Zhuo et al. revealed that MIP-1α and IP-10 from activated monocytes and macrophages trigger progression of cytokine storm in patients with severe Covid-19 [80].

As results, high PRL serum level may increase Covid-19 severity by augmentation and release of MIP-1α and IP-10. Besides, a prospective cohort study illustrated that Covid-19 patients are associated with reduction of circulating T, B, and NK cell with macrophage cytotoxicity that reduce the antiviral activity mainly in Covid-19 patients in ICU due to high IL-6 serum level and induction of oxidative stress [81].

Moreover, perturbation of Treg in Covid-19 is correlated with disease severity and complications due to reduction of anti-inflammatory cytokines from Treg [82].

Indeed, Song et al. divulge that auto-reactivity of T and B cells is triggered in Covid-19 with risk of autoimmunity [82]. Therefore, high PRL serum level may increase severity of Covid-19 through activation of immune cells cytotoxicity, release of pro-inflammatory cytokines, inhibition of Treg cells, and induction of B cell auto-reactivity (Fig. 6).

The underlying mechanisms of high PRL serum level in Covid-19 are poorly understood, although stress, oxidative,

and immune dysregulation could be the potential mechanisms, since stressful conditions in Covid-19 may trigger release of PRL [83]. In a precise manner, dopamine which is an inhibitory releasing factor for PRL release is involved in the pathogenesis of SARS-CoV-2 during CNS invasion [84, 85].

It has been shown that there is co-expression of ACE2 and dopa decarboxylase (DDC), which is an enzyme responsible for synthesis of dopamine and serotonin [86]. As well, ACE2 regulates DDC activity through formation of AngI1-7 [86], therefore downregulation of ACE2 by SARS-CoV-2 may alter dopamine and serotonin biosynthesis [86]. Therefore, reduction of brain dopamine by SARS-CoV-2 can remove the inhibitory effects on PRL leading to hyperprolactinemia as seen in Covid-19 patients.

Mpekoulis et al. observed that expression of DDC with ACE2 is also observed in nasopharyngeal tissue [87]. Indeed, monocyte also expresses DDC which regulates synthesis of dopamine [88].

In Covid-19, lymphopenia and dysregulation of monocyte/macrophages may affect the expression and activity of DDC [89]. Therefore, downregulation of central and peripheral DDC may increase hypothalamic PRL and extra-pituitary PRL leading to hyperprolactinemia in Covid-19.

Furthermore, high inflammatory milieu in Covid-19 could be a proposed mechanism for high PRL serum, since high IL-6 serum in Covid-19 is regarded as a potent stimulator for PRL from anterior pituitary [90, 91]. Previous study revealed that stress induced by immune activation and hyperinflammation may provoke release of PRL from anterior pituitary [92]. Experimental study demonstrated that
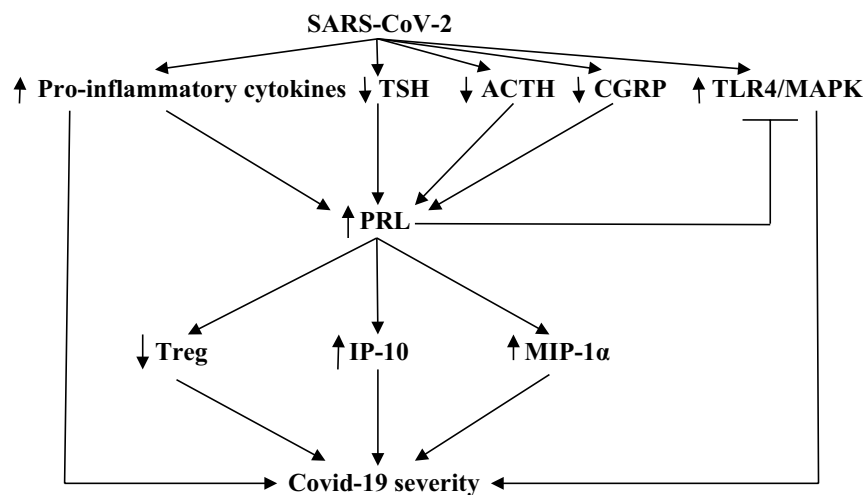

Fig. 6 Prolactin (PRL) and Covid-19 severity: SARS-CoV-2 induces activation of pro-inflammatory cytokines, toll-like receptor 4 (TLR4), and mitogen-activated protein kinase (MAPK), with inhibition of thyroid-stimulating hormone (TSH), adrenocorticotropic hormone (ACTH), and calcitonin gene-related peptide (CGRP) leading to activation of PRL release, which in turn stimulate inflammatory protein-1α (MIP-1α) and interferon protein 10 (IP-10) with inhibition of regulatory T cell (Treg), leading to hyperinflammation and Covid-19 severity
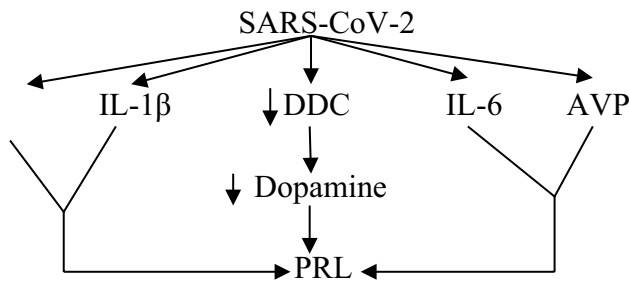
Fig. 7 Mechanism of hyperprolactinemia in Covid-19: Prolactin (PRL) increases angiotensin II (AngII), IL-1β, IL-6, and arginine vasopressin (AVP) with reduction of dopa decarboxylase (DDC), with subsequent increase of PRL

administration of bacterial endotoxin activates PRL from anterior pituitary through inhibition of hypothalamic dopamine and activation of corticotrophin releasing factor (CRF) at hypothalamus [93].

Besides, pro-inflammatory cytokines mainly IL1β cross BBB and activate release of PRL from anterior pituitary in rat [94]. Moreover, a follicular stellate cell of anterior pituitary is regarded as a source and target for pro-inflammatory cytokines including TNF-α, IL-1, and IL-6 during systemic inflammatory conditions [95]. As well, anterior pituitary cells express TLR4, which involve in PRL release and development of prolactinoma by stimulatory effects of estrogen [96].

Haj-Mirzaian et al. showed that higher activity of HPA axis TLR4 is associated with chronic stress and may lead to inflammation-induced cardiovascular and metabolic disorders [97]. In addition, activation of central TLR4 can inhibit hypothalamic gonadotropin-releasing hormone (GnRH), which stimulate PRL release [98]. Therefore, high pro-inflammatory cytokines and activated TLR4 in Covid-19 may lead to activation release of PRL from anterior pituitary and could explain hyperprolactinemia in Covid-19.

On the other hand, downregulation of ACE2 by SARS-CoV-2 leads to reduction of vasodilator Ang1-7 and Ang1-9 with increment in the level of vasoconstrictor AngII [99]. It has been reported that AngII is regarded as a powerful activator of PRL release from anterior pituitary [100]. Similarly, arginine vasopressin (AVP) activates release of PRL from anterior pituitary during stress in peripartum period [101].

Recently, Al-kuraishy et al. [102] illustrated that AVP is augmented in Covid-19 due to high circulating AngII and pro-inflammatory cytokines. Thus, high AVP and AngII serum levels during Covid-19 might be another possible mechanism for Covid-19-induced hyperprolactinemia (Fig. 7).

Furthermore, these studies revealed that high PRL serum level in Covid-19 could have protective and harmful effects according to the phase of SARS-CoV-2 infection. High PRL serum level in Covid-19 might be a compensatory mechanism to counteracting hyperinflammation and associated endocrinopathies.

The present study has several limitations including paucity of clinical studies regarding PRL serum level in Covid-19 patients. As well, in silico, experimental and clinical trial studies concerning role of PRL were not evaluated. However, this study gives an explanation for the potential role of PRL in Covid-19 and proposed mechanisms for high PRL serum level in Covid-19. Although, experimental, clinical trial and clinical studies are necessary in this regard to confirm the inflammatory and/or anti-inflammatory role of PRL in Covid-19.

Conclusion

In Covid-19, there are noteworthy immunological and inflammatory changes that are affecting neuroendocrine homeostasis mainly in older patients with underlying co-morbidities. Of interest PRL has anti-inflammatory effects by attenuating expression TLR4 and NF-κB with succeeding decrease in the release of pro-inflammatory cytokines. In addition, Covid-19-induced stressful status may affect release of PRL and other stress-mediated hormones. On the other hand, PRL may has a pro-inflammatory agent increase release of pro-inflammatory cytokines and development of immunoinflammatory disorders. Therefore, high PRL serum level may increase severity of Covid-19 through activation of immune cells cytotoxicity, release of pro-inflammatory cytokines, inhibition of Treg cells, and induction of B cell auto-reactivity. The underlying mechanisms of high PRL serum level in Covid-19 are poorly understood, although stress, oxidative, and immune dysregulation could be the potential mechanisms, since stressful conditions in Covid-19 may trigger release of PRL. High PRL serum level in Covid-19 might be a compensatory mechanism to counteracting hyperinflammation and associated endocrinopathies. Besides, high pro-inflammatory cytokines and elevated TRH, AngII and AVP in Covid-19 could be proposed mechanisms for Covid-19-induced hyperprolactinemia. Nevertheless, experimental, clinical trial, and clinical studies are necessary in this regard to confirm the inflammatory and/or anti-inflammatory role of PRL in Covid-19.

Data availability Not applicable.

Code availability Not applicable.

Declarations

Conflict of interest The authors declare no conflict of interest.

Ethical approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

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