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The effects of prolactin on the immune system, its relationship with the severity of COVID-19, and its potential immunomodulatory therapeutic effect

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ABSTRACT

Prolactin (PRL) is an endocrine hormone secreted by the anterior pituitary gland that has a variety of physiological effects, including milk production, immune system regulation, and anti-inflammatory effects. Elevated levels of PRL have been found in several viral infections, including 2019 coronavirus disease (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV2), a viral pathogen that has recently spread worldwide. PRL production is increased in SARS-CoV2 infection. While PRL can trigger the production of proinflammatory cytokines, it also has several anti-inflammatory effects that can reduce hyperinflammation. The exact mechanism of PRL's contribution to the severity of COVID-19 is unknown. The purpose of this review is to discuss the interaction between PRL and SARS-CoV2 infection and its possible association with the severity of COVID-19.

1. Introduction

Prolactin (PRL) is a lactogenic hormone produced by the anterior pituitary gland. It plays a critical role in milk production and also contributes to immune system control. PRL release is regulated by dopamine, which limits its release through dopamine receptor type 2, and by hypothalamic-releasing factors, which promote its release from the anterior pituitary gland [1]. Thyrotropin-releasing hormone (TRH) and estrogen may stimulate PRL synthesis [2]. PRL exerts its effects through its specific receptors, known as PRL receptors (PRLRs). These receptors also act as receptors for other cytokines, such as interleukin-6 (IL-6) [3]. It can also regulate the immune system by activating cytokine receptors [4]. The diverse functions of PRL are mediated by the activation of various types of receptors, including PRLRs and cytokine receptors [5]. Furthermore, PRL can regulate the immune system by activating cytokine receptors [4]. Elevated PRL production has been observed in various viral infections [6]. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel viral pathogen, has rapidly spread worldwide and infected a significant number of individuals [7]. Studies have reported an increase in PRL synthesis during SARS-CoV-2 infection. PRL may contribute to the production of pro-inflammatory cytokines and exacerbate the infection. However, PRL also has several anti-inflammatory effects and may help to reduce hyper-inflammation associated with SARS-CoV-2 infection [8]. The present research

Abbreviations: PRL, prolactin; TRH, thyrotropin-releasing hormone; PRLRs, prolactin receptors; IL-6, interleukin-6; SARS-CoV2, Coronavirus type 2; HIV, human immunodeficiency virus; PKA, cAMP/protein kinase A; TNF-α, tumor necrosis factor-alpha; SLE, systemic lupus erythematosus; RA, rheumatoid arthritis; ROS, reactive oxygen species; HCMV, human cytomegalovirus; RSV, syncytial viral disease; HPA, hypothalamic-pituitary-adrenal; ALI, Acute lung injury; PIF, Prolactin inhibitory factor; T3, releasing hormone; TRH, prolactin-releasing factor; PRF, peripheral blood mononuclear; IFN-γ, PBMC interferon-γ; IDDM, Insulin-dependent diabetes mellitus; HCMV, Human cytomegalovirus; ALI, Acute lung injury; ERK1/2, Extra-cellular signal-regulated kinase ½; TIDA, Tuberoinfundibular dopamine.

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provides information on PRL's immune system effects, its association with COVID-19 severity, and its possible immunomodulatory therapeutic impact.

2. Prolactin secretion and function

PRL is primarily synthesized and released by the anterior pituitary gland, but can also be produced by other tissues such as the mammary glands, uterus, immune system, and central nervous system [1]. Triggering of PRL production in these tissues can be induced by stress, odor, nipple stimulation, and light. Other molecules can also stimulate PRL production, including dopamine antagonists, estrogen, and thyrotropin-releasing hormone (TRH) [1].The expression of PRL in the pituitary gland mainly relies on the adaptation of inhibitory and stimulatory molecules such as hormones, cytokines, and alternative factors that coordinate a cascade of intracellular events involving various signaling pathways. Among all these signaling cascades, cAMP/protein kinase A (PKA), phosphatidylinositol/Ca++/protein kinase C (PKC), and mitogen-activated protein kinase (MAPK) stand out. In addition, it appears that the PRL gene follows pulsatile transcriptional dynamics with refractory phases during transcriptional cycles [9].

In the pituitary gland, a direct correlation between transcribed mRNA and released protein cannot be established because numerous posttranscriptional changes can influence final protein production; these include mRNA degradation, protein storage, and secretion regulation. PRL secretion via the pituitary gland depends on the action of secretagogues, which stimulate the lactotroph cell membrane and rapidly release stored PRL via calcium-dependent exocytosis regulated at the level of transcription [10]. Moreover, other hormones regulate PRL secretion from the hypothalamus, such as dopamine and primary physiological prolactin inhibitory factor (PIF). In addition to the effect of PRL on thyroid function, triiodothyronine (T3) inhibits the human PRL gene promoter and is likely involved in PRL secretion. Interestingly, T3-releasing hormone (TRH) plays the opposite role and acts as prolactin-releasing factor (PRF). PRL also has a negative feedback on its secretion by activating tuberoinfundibular dopamine (TIDA) cells through its binding to PRLR on these neuronal cells [11]. PRLRs form a complex receptor system associated with more than 300 biological mechanisms such as cell differentiation, cell reproduction, and immune responses. PRLRs are a type of cytokine receptor that shares a common structural motif called the cytokine receptor homology domain (CRH) [12].

They can be activated by three sequentially distinct proteins: PRL, placental GH and lactogenic [13]. PRLRs are found in a variety of cells and tissues, such as the brain, breast tissue, prostate, placenta, seminal vesicles, immune system, all leukocytes, and thymus [14].Some studies have reported the essential role of the downstream signaling cascade (PRLR/Jak2-Stat5) and PRL in the development of various aspects of mammary gland differentiation and lactation [13]. Thus, the primary functions of PRL include mammary gland vesicle development and milk production. PRL stimulates mammary alveolar cells to produce milk components such as lipids, casein, and lactose. During pregnancy or when progesterone levels increase, PRLR is downregulated in breast tissue [13].

3. Prolactin and the immune system

PRL has a variety of effects on the regulation of the immune system [4,15]. It is thought to be produced by T and B cells, which enhance the autocrine and paracrine effects of PRL in the immune system [16] and to exhibit cytokine-like activity in human mononuclear and polymorphonuclear leukocyte cells [17]. In addition, PRL is produced by macrophages and also has a high concentration of PRLRs [18]. In the immune system, PRLR expression has been analyzed in various cells such as splenocytes, thymocytes, bone marrow cells, peripheral blood mononuclear cells (PBMCs), lymphocytes, and monocytes [19]. Both PRL and its receptors are constitutively expressed by resting T cells [16], which may influence the immune system even under constant conditions. Autocrine PRL behavior could be explained by PRLR alteration. According to some in vitro studies, lymphocytes are a major target tissue for circulating prolactin. On the surface of lymphocytes, interleukin-2 receptors are induced by concanavalin-A-natured PRL. This triggers ornithine decarboxylase and activates the enzyme protein kinase C, which plays a critical role in lymphocyte differentiation, proliferation, and function. Lymphocyte proliferation is inhibited by PRL antibodies. In addition, expression of certain co-stimulatory fragments (CD137, CD154) and secretion of some other cytokines induced by hypothalamic-pituitary-adrenal (HPA) activation have also been observed in these cells [20]. Although it has been observed that PRL interacts with IL-2, there is evidence that PRL can act independently of IL-2 as a growth factor for T cells [21]. Moreover, PRL has been shown not only to stimulate proliferation but also to inhibit apoptosis of lymphocytes [22]. In BALB/c mice, a heavy chain transgene for a pathogenic anti-DNA antibody stimulates a twofold increase in serum PRL levels, increases autoreactive B cells with a follicular phenotype, and accelerates their activation with subsequent anti-DNA antibody production and IgG deposition in the kidneys [23]. On the other hand, PRL has several immunomodulatory effects on the immune system. Researchers determined the effect of PRL in hypophysectomized rats and concluded that PRL increased weight gain in two lymphoid tissues, the spleen and thymus [24]. In lymphocytes, PRL abolishes various hypophysectomy-induced pathologies, such as anemia, leukopenia, and thrombocytopenia, and accelerates antibody production. It has also been confirmed that PRL modulates the levels of IL-2 and PRL receptors [19]. Notwithstanding the immunomodulatory role of PRL, immune system development was not impaired in both PRL and PRLR knockout mice [25]. The response attributable to a lack of PRL activity may be to compensate for an excess of cytokine networks. PRL plays an immunomodulatory role in normal cells of mice and humans and in in vivo models after procedures such as hypophysectomy and ovariectomy. Further studies are needed to analyze the involvement of PRL in physiological and/or pathological conditions and to investigate its therapeutic effect in immune system diseases.

4. Prolactin's impacts on inflammation and inflammatory cytokines

PRL is thought to function in the immune system as a locally assembled cytokine important for immune regulation and modulation of T and B cell functions. However, the molecular arrangement that modifies PRL expression, along with various elements that play roles in the immune system, is not fully understood. Structural analysis of PRL and its receptors has revealed their relationship to the cytokine/hematopoietic family. PRL is produced by lymphocytes, thymocytes, mononuclear and natural killer cells in the immune system. Moreover, PRL secretion is mainly associated with the T lymphocyte fraction in PBMCs [26]. Since it uses its own promoter, PRL expression in lymphocytes is independent of Pit-1 and other related hormones such as progesterone, estrogen, TRH, dihydrotestosterone, insulin, and some other classical PRL modulators in the pituitary gland. In contrast, PRL expression in T lymphocytes is stimulated by cAMP, retinoic acid, and calcitriol, while it is inhibited by dexamethasone and some interleukins in an autocrine and paracrine manner [26-28]. Furthermore, IL-2, IL-1b and IL-4 decreased PRL mRNA, while IL-10 and interferon-γ (IFN-γ) had no effect on it [27]. Nevertheless, a proinflammatory cytokine such as tumor necrosis factor-alpha (TNF) modulated the alternative PRL promoter in myeloid leukemia cells. A TNF-responsive region is located between 1842 and 1662 of the extrahypophyseal PRL promoter. Surprisingly, an enzyme, PKC inhibitor, inhibited the stimulatory effect of TNF on PRL [28]. Since TNF is a known pro-inflammatory cytokine, its involvement in PRL stimulation may have clinical implications, as some studies have shown that leukocyte-derived PRL is directly involved in autoimmune and hematologic pathologies [29]. Several molecular species are formed after post-translational modifications of the PRL molecule. A correlation

between PRL levels and anti-dsDNA antibodies and between anti-Ro and anti-La antibodies has been established [30]. A balance between the two arms of the cellular immune response is involved in the physiology of the immune system. The cellular and humoral responses were initiated by type 1 (Th1) and type 2 (Th2) T helper cells, respectively. PRL is involved in balancing Th1 and Th2 responses. Altered PRL levels associated with either Th1 or Th2 dominance are often characteristic of autoimmune diseases. Evidence from animal models and human disease suggests that Th1 cytokines (IFN-γ, IL-2, and TNF) are involved in the development of organ-specific autoimmune diseases such as RA, MS, insulin-dependent diabetes mellitus (IDDM), and thyroid autoimmunity. In contrast, Th2 responses may be involved in the development of diseases such as SLE and systemic and allergic diseases such as HT [31].

4.1. Inflammatory signaling pathways activated by prolactin

Due to the presence of numerous enhancer and silencer domains, the control of PRL gene expression is quite complex, and chromatin loop formation has implications for transcriptional dynamics. Chromatin loop formation has implications for transcriptional dynamics. Two promoters with different responses can act on regulatory mediators that control PRL transcription in a cell type-specific manner [9]. Early biochemical evidence for PRL stimulation is the rapid and transient phosphorylation of specific cellular proteins, such as Janus kinases (JAKs) and PRLR [32]. It has been reported that a type of signaling pathway is involved not only in the immune response of numerous cytokines, but also in the effects of mainly non-immune mediators such as growth factors and hormones, which are considered JAK /signal transducers and activators of transcription (STAT)-signaling pathway [33]. Activated protein tyrosine kinases (PTKs) and JAKs phosphorylate the cytoplasmic domain of the receptor by creating recruitment sites for signaling proteins such as STAT, which are phosphorylated by JAKs that are dimerized and translocated to the nucleus where they regulate gene expression [34]. Proteins of the STAT family are involved in cytokine-mediated biological responses [35]. Different types of STAT -family proteins such as STAT1, STAT3 and STAT5 are common mediators of PRL signaling in various cells of lymphoid, myeloid and mammary epithelia [36]. Moreover, PRL is responsible for the significant activation of p91/ STAT-1 in Nb2 cells of rat prelymphomas [37]. STAT3 knockout mice are highly exposed to endotoxin shock, and macrophages from these mice atypically produce excessive levels of pro-inflammatory cytokines in response to endotoxin [38]. STAT3 proteins can mediate anti-inflammatory responses in macrophages [39] MAPKs are crucial intracellular signaling networks utilized by eukaryotic cells in aspects of signal transduction stimulated by a wide range of extracellular stimuli. Originally, small-molecule protein kinases were reported to be rapidly activated after stimulation with a variety of mitogens. In recent years, several cellular stressors that activate serine/threonine kinases have been investigated. All MAPKs are proline-directed serine/threonine protein kinases activated by phosphorylation of threonine and tyrosine residues in the Thr-X-Tyr motif in the activation loop located near the ATP and substrate binding sites [40].

The c-Jun N-terminal kinase (JNK) enzyme phosphorylates serine residues at positions 63 and 73 in the N-terminal of c-Jun [41], producing an immediate early gene product that is a member of the AP1 transcription factor complex [42]. JNKs are also considered stress-activated protein kinases as they are stimulated by a range of cellular stresses such as UV light, antioxidants, reactive oxygen species (ROS), heat, hyperosmotic shock, protein synthesis inhibitors, and pro-inflammatory cytokines [43]. The mechanism of activation of JNK MAPKs is highly complicated and is still being decoded. The major group of phagocytic leukocyte cells might be composed of macrophages that play a critical role in host immune-control reactions against invading pathogens and malignancies [44]. Activated macrophages can act as accessory cells, antigen-presenting cells, and sources of cytokines for the activation of other immune effector cells [45]. The major cytokines produced by macrophages are pro-inflammatory like IL-1b, TNF, IFN, and IL-12 and are central to their regulatory role or in the orchestration of a robust immune response by macrophages [46]. Activated macrophages produce reactive oxygen and nitrogen intermediates in addition to cytotoxic cytokines (IL-1 and TNF) [47]. The cytotoxicity of macrophages against tumor cells has been extensively studied [48], and it has been discovered that activated macrophages can kill tumor cells through direct cell-to-cell contact or by secreting effector molecules such as reactive nitrogen intermediates and TNF [49]. In addition, PRL has been shown to increase the cytotoxicity of NK cells against tumor cells in vivo and in vitro [50]. Therefore, to clear the infection, an appropriate balance of effector molecules produced during infection and phagocytosis is important to avoid triggering an excessive inflammatory response, which may lead to pathological conditions in the host [51].

5. Prolactin and viral infections

Hyperprolactinemia, i.e., high serum PRL levels, and human immunodeficiency virus (HIV) infection have been reported to go hand in hand. The use of antiretroviral therapy, viral load, metabolic problems, liver disorders, or hyperprolactinemia in HIV infection are not related [8]. Observational studies of 192 HIV-positive men have shown that hyperprolactinemia occurs in 21.4% of these patients and is related to higher CD4+ cell counts [8,52]. Furthermore, human cytomegalovirus (HCMV) promotes the expression of PRLRs in ovarian cancer by activating inflammatory cascades such as MAPK and NF-κB, and by suppressing anti-inflammatory pathways and triggering inflammatory pathways that further promote viral replication and exacerbate inflammatory responses, HCMV and PRL may share an identical immunological pathway [53]. Wallis showed that PRLRs could serve as a receptor and entry site for virus-host cell communication for CMV and other viruses such as rubella [54]. In addition, a prospective study showed increased PRL serum levels in patients with hepatitis C virus (HCV) compared with control groups, which was due to HCV induction of PRL mRNAs in PBMC [55]. Although this association does not include extrahepatic manifestations of HCV such as autoimmunity, hyperprolactinemia is associated with HCV [56]. In addition, 32 hospitalized infants with respiratory syncytial virus (RSV) disease were included in a prospective cohort study that showed an association between severe RSV infection and high serum PRL levels and lymphopenia [57]. In addition, during the 2003 SARS pandemic, SARS-CoV led to a sharp increase in serum PRL levels as a result of dysregulation of adenopituitary control caused by a direct cytopathic effect or associated pro-inflammatory changes [58].

The involvement of PRL in the pathophysiology of viral entry and replication and the stimulation of PRL secretion through the associated induction of inflammatory signaling pathways explain the increased PRL serum class in various viral diseases. However, because of the anti-inflammatory properties of PRL, the elevated PRL serum levels in viral diseases may represent a compensatory strategy.

6. Mechanism of SARS-COV-2 infection on the prolactin release

Although the causes of the increased serum levels of PRL at COVID-19 are not well understood, stress, oxidative stress, and immunologic dysregulations may contribute. Thus, COVID-19 may release PRL under stressful circumstances [59]. In addition, studies based on the stage of SARS-CoV-2 infection have shown that excessive serum levels of PRL at COVID-19 can have both beneficial and detrimental effects. Significant inflammatory and immunologic abnormalities during SARS-CoV2 infection primarily affect elderly patients with underlying comorbidities and impair neuroendocrine balance. In addition, the stress state induced by COVID-19 may affect the release of PRL and other stress-related hormones [60]. One study suggests that PRL release from the anterior pituitary may be activated by immune hyperactivity and the inflammatory response to COVID-19 [61]. For example, an elevated IL-6

serum level at COVID-19 is probably an effective activator of PRL release from the anterior pituitary [62,63]. A highly inflammatory situation at COVID-19 could be a possible mechanism for high serum PRL levels. Moreover, pro-inflammatory cytokines, especially IL1, cross the blood–brain barrier and stimulate PRL release from the anterior pituitary in rats [64]. In addition, follicular stellate cells of the anterior pituitary are thought to be a source and target of pro-inflammatory cytokines such as TNF, IL-1 and IL-6 during systemic inflammatory states [65]. The anterior pituitary cells express TLR4, which is involved in PRL release [66]. Petrulli et al. showed that systemic inflammation activates striatal dopamine, leading to a decrease in PRL secretion [67]. Sen suggested that dopamine antagonists may increase the production of the immunostimulatory PRL in COVID-19, thereby improving immune activity [8]. Hypothalamic TRH acts as an effective stimulant of PRL release in the anterior pituitary [68]. In this context, a prospective observational clinical study of 31 men receiving infertility treatment during blocking COVID-19 in Italy showed that TSH was dramatically decreased by an unknown mechanism [69].

In COVID-19, low serum TSH levels may cause the hypothalamus to produce TRH, followed by the anterior pituitary releasing PRL. Also, previous studies examining sperm quality in 41 men with COVID-19 found that their serum PRL levels increased and remained elevated after recovery [70]. These results suggest that SARS-CoV-2 virus may affect the hypothalamic-pituitary-gonadal axis and enhance PRL production by the anterior pituitary in SARS-CoV-2 infection. In addition, there are significant interactions between COVID-19 infection and the HPA axis due to stimulation of the HPA axis by stress and pro-inflammatory cytokines that regulate the body's response to inflammatory mediators [71]. A prospective cohort study of COVID-19 cases found that cortisol and ACTH blood levels were significantly lower in COVID-19 infections, indicating an impaired adrenocortical response due to central adrenal insufficiency [71]. Based on experimental studies, individuals with adrenal hormone deficiency have higher serum PRL levels [68,72]. In addition, 21 (8.5%) of the 235 SARS-CoV-2 cases in the cross-sectional analysis by Kumar et al. had hyperprolactinemia without sex difference, and this situation was not related to the severity or mortality of COVID-19. Furthermore, 25.1% of COVID-19 cases had primary hypothyroidism [73], comparable to the euthyroid state observed in viral infections [74]. A retrospective study including 54 COVID-19 cases found a correlation between low free T3 levels and the likelihood of mechanical ventilation [75]. These results suggest that hyperprolactinemia in SARS-CoV-2 disease may be stress-induced, with no correlation between COVID-19 severity and PRL levels in the absence of other endocrinopathies. However, the severity of COVID-19 correlates with secondary hyperprolactinemia in individuals with adrenal insufficiency or hypothyroidism. A previous cohort study found that patients with septic shock-induced acute lung injury (ALI) had higher blood PRL levels [76]. PRL is essential for the control of inflammatory and immunological responses. Nevertheless, an experimental study showed that domperidone, a dopamine antagonist, causes ALI by exacerbating inflammation-induced damage to airway epithelial cells when repeatedly administered to experimental mice [77]. Moreover, the anti-inflammatory and bronchoprotective effects of calcitonin gene-related peptide (CGRP), its vasodilatory properties, and tissue repair have been demonstrated [68].Immunological dysregulation reducing serum CGRP levels at COVID-19 was demonstrated by Ochoa-Callejero et al [78]. Similarly, CGRP deficiency leads to the development of autoimmunity due to PRL overexpression and deficiency of anti-inflammatory cytokines [79]. Thus, decreased CGRP activity can lead to increased PRL levels in serum samples from COVID-19 (Fig. 1).

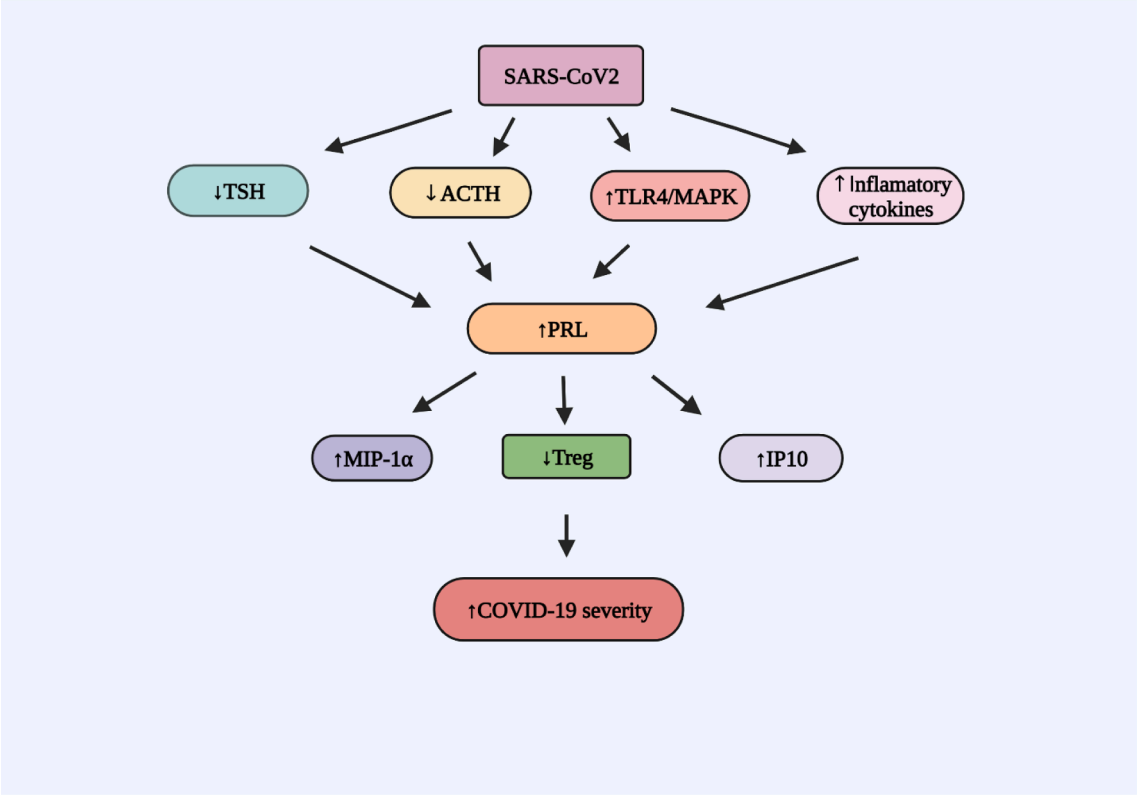

Fig. 1. Prolactin (PRL) and severity of covid-19. SARS-CoV-2 stimulates the production of pro-inflammatory cytokines, Toll-like receptor 4 (TLR4), and mitogen-activated protein kinase (MAPK) while inhibiting the release of thyroid-stimulating hormone (TSH), calcitonin gene-related peptide (CGRP), and adrenocorticotropic hormone (ACTH), leading to activation of PRL release. As a result, PRL stimulates the release of inflammatory protein-1α (MIP-1α) and interferon protein 10 (IP-10) while inhibiting regulatory T cells (Treg), leading to hyperinflammation and COVID-19 severity.

7. Effects of prolactin on COVID-19 severity

PRL can either cause or reduce inflammation depending on the underlying medical conditions [68,80]. Thus, COVID-19 could benefit from the anti-inflammatory effects of PRL by reducing overactive immune responses. It has been difficult to demonstrate the anti-inflammatory effects of PRL in SARS-CoV-2 infections because there have been few and limited exploratory and clinical phase studies. Note that PRL inhibits the production of NF-κB and TLR4, thereby reducing the release of pro-inflammatory cytokines [68]. Interestingly, PRL can reduce inflammation by increasing the immunosuppressive hormone progesterone [81]. When TLR4 and NF- κB are turned on and increased in COVID-19, pro-inflammatory cytokines are released and ALI, acute respiratory distress syndrome (ARDS), occurs [82].

In 2020, Pinna made the following claim: sex steroids, especially progesterone, have immunological, regulatory, and anti-inflammatory effects that protect women from COVID-19 and may play a role in COVID-19 the development of disease in postmenopausal women [83].

Devi et al. discovered that PRL suppresses MAPK expression in the ovary with the progression of premature ovarian failure [84]. As a result, PRL can prevent immunological thrombosis and endothelial cell dysfunction caused by MAPK in COVID-19 [85]. In contrast, PRL is considered to be a pro-inflammatory agent that develops immunological and inflammatory diseases and increases the production of inflammatory secretions. Specifically, PRL causes the production of ROS, increasing the cytotoxicity of macrophages [86]. PRL triggers the secretion of interferon protein-10 (IP-10), chemokines, macrophage cell inflammatory protein-1α (MIP-1α), and monocyte chemoattractant protein-1 (MCP-1) [87].

According to Zhuo et al, IP-10 and MIP-1α from activated monocytes and macrophages develop a cytokine storm during severe SARS-CoV-2 infection [88]. Consequently, elevated levels of PRL in serum may increase and secrete IP-10 and MIP-1α, which may exacerbate the severity of COVID-19. In addition, PRL induces NK cells to produce INF -γ by stimulating T cells and producing proinflammatory molecules [89]. In addition, the function of Treg cells is inhibited by PRL [8]. PRL induces autoreactivity of B cells, which stimulates the formation of antibodies [68]. Therefore, immunological dysregulation in SARS-CoV-2 infections is significantly influenced by inflammatory signaling cascades. A cohort study has shown that COVID-19 cases have lower levels of circulating NK, B, T, and macrophage cytotoxicity cells, which reduces antiviral activity, especially in COVID-19 cases in the ICU, where IL-6 levels are high and oxidative stress is induced [90]. Moreover, disruption of Tregs at COVID-19 is associated with disease severity and outcome due to a decrease in anti-inflammatory mediators of Tregs [91]. Song et al. demonstrated that COVID-19 triggers autoreactivity of B and T lymphocytes, which poses an auto-immunological risk. Due to activation of immune cell cytotoxicity, production of pro-inflammatory secretions, suppression of Treg lymphocytes, and promotion of autoreactivity of B cells, high levels of PRL may exacerbate COVID-19 [91].

7.1. Potential molecular mechanism of prolactin in COVID-19

The main molecular mechanism of the high PRL level in COVID-19 is not well known. Dopamine is a PRL inhibitory factor that plays a critical role in the pathogenesis of SARS-CoV-2 in the nervous system. Dopa decarboxylase, an enzyme involved in dopamine synthesis, is co-expressed with angiotensin-converting enzyme 2 (ACE2). During SARS-CoV2 infection, ACE2 expression is decreased, which impairs dopamine and serotonin synthesis. Therefore, lowering dopamine levels under conditions of viral infection abolishes the inhibitory effect of dopamine on PRL release [92]. By lowering the level of dopamine under the conditions of viral infection, the inhibitory effect of dopamine on PRL release is abolished. As a result, hyperprolactinemia occurs in COVID-19 patients. Activation of central TLR4 can inhibit hypothalamic gonadotropin-releasing hormone (GnRH), which stimulates PRL release [93]. Therefore, high levels of pro-inflammatory cytokines and activated TLR4 might trigger the release of PRL from the anterior pituitary, which could explain the hyperprolactinemia at COVID-19. On the other hand, the reduced expression of ACE2 by SARS-CoV-2 decreases the vasodilator angiotensin (Ang) 1–7 and increases the vasoconstrictor Ang II [94]. According to the literature, Ang II is a potent activator of PRL release from the anterior pituitary [95,96]. In particular, due to the underlying pathological processes, PRL has both inflammatory and anti-inflammatory effects. PRL activates its specific receptor, which stimulates the pro-inflammatory signaling pathway, resulting in inflammatory or anti-inflammatory effects [6,97]. The activation of PRL receptors can stimulate various inflammatory pathways such as PRLRs extracellular signal-regulated kinase 1/2 (ERK1/2), MAPK, STAT5, and JAK2. Activation of PRLRs can trigger inflammatory or anti-inflammatory processes. Activation of these pathways depends on the activated isoform of PRLRs. PRL can activate JAK2/STAT1 signaling in the macrophage, leading to the production of inflammatory cytokines such as TNF, INF -γ, IL-1β, and IL-12. In addition, PRL can induce STAT3 activation, leading to the production of IL-10, an anti-inflammatory cytokine [98]. The expression of TLR4 and NF- κB is increased in COVID-19 infection, which enhances the production of pro-inflammatory cytokines and the development of ARDS. The anti-inflammatory role of PRL in COVID-19 may be beneficial by reducing excessive immune responses. PRL has an anti-inflammatory effect by decreasing the expression of TLR4 and NF-κB, which leads to a decrease in the production of pro-inflammatory cytokines [99,100]. The anti-inflammatory effect of PRL may be due to an increase in progesterone as an immunosuppressant. In addition, it was discovered that PRL can inhibit a number of inflammatory processes activated by the MAPK pathway during COVID-19 infection [84]. Thus, PRL could inhibit MAPK-mediated endothelial dysfunction and immune thrombosis in COVID-19. Therefore, the high serum PRL level at COVID-19 might be a compensatory mechanism for the activated TLR4/NF-B/MAPK axis and low progesterone in COVID-19 [6].

7.2. Pathophysiologic features of COVID-19 associated with abnormal prolactin levels

In contrast to the various recognized anti-inflammatory effects of PRL, PRL is considered a pro-inflammatory mediator and can promote inflammatory pathological effects in cells and tissues. Remarkably, PRL can induce the secretion of IP-10, macrophage inflammatory protein-1 (MIP-1α), various chemokines, and MCP-1 from activated macrophages. PRL can trigger T-cell activation leading to NK cell activation and inflammatory cytokine production. In addition, PRL can stimulate B cell activation to produce antibodies [101]. Thus, multiple factors influence the signaling pathways of the inflammatory process, leading to immune deregulation during COVID-19. According to one study, MIP-1α and IP-10 produced by macrophages cause the development of cytokine storm in COVID-19 patients [88]. Elevated PRL levels may exacerbate the severity of COVID-19 disease by inducing the secretion of MIP-1 and IP-10 [92]. Therefore, some studies suggest that high PRL levels may worsen disease severity by inducing inflammatory cytokines and stimulating B cell autoreactivity. These studies also showed that high serum PRL level at COVID-19 could have protective and deleterious effects depending on the phase of SARS-CoV-2 infection [6].

8. Prolactin difference between the two sexes and COVID-19 severity

The relationship between prolactin levels, sex differences, and the course of SARS-CoV-2 infection is an interesting topic of discussion. PRL levels clearly vary between men and women. In general, females have higher prolactin levels due to its role in lactation and breast development [102].

Research indicates that gender differences play a role in the susceptibility, severity, and consequences of SARS-CoV-2 infection. Men

are more likely than women to develop severe COVID-19 symptoms and have an increased risk of death. These differences could be related to a variety of factors, including hormonal changes, immune system responses, and lifestyle factors [103]. There is evidence that prolactin has immunomodulatory properties, meaning that it may influence the immune system's response to infection [104]. In this context, it is possible that different prolactin levels in men and women could contribute to the observed sex differences in disease progression [8]. It is important to consider other factors, such as the influence of sex hormones like estrogen and testosterone, which also have immunomodulatory effects and could influence the immune response to SARS-CoV-2 in the women [105]. Although there is evidence for the influence of sex differences on SARS-CoV-2 infection, the specific role of prolactin in this context has not yet been clearly elucidated. Further research is needed to better understand the complex interactions between hormones, the immune system and the progression of COVID-19.

9. Prolactin as a potential immunomodulatory therapy for COVID-19

PRL is a protein that is also secreted by lymphocytes and acts through the same signaling pathway as cytokines [4]. This protein plays an active role in both cellular and humoral immunity [106,107]. PRL-T stimulates the proinflammatory response through helper 1 cells. Women have higher levels of PRL, and autoimmune diseases (such as systemic lupus erythematosus and multiple sclerosis) are more common in women than in men. The ability of bromocriptine, a dopamine agonist, to suppress these diseases by lowering PRL levels is also related to this situation [107-109]. The immunostimulatory PRL may have immunosuppressive effects in higher doses under certain conditions [110,111]. PRL can support innate immunity by stimulating neutrophils, macrophages, natural killer cells, and dendritic cells, and can also increase the expression of TLR (Toll-like receptor) [112,113]. High levels of PRL are a good prognostic factor in patients with sepsis and show this effect by stimulating natural and acquired immunity [114,115]. Survival can be increased by stimulating the immune system with agents that antagonize dopamine. In view of this information, immunomodulation via PRL levels is a potential area of research as it can reduce morbidity and mortality in the prognosis of COVID-19. In a study conducted in France, chlorpromazine, which is a dopamine antagonist and naturally increases PRL levels in patients' blood, was shown to be less affected by COVID-19 than medical personnel [116]. Drugs of the SSRI group and tricyclic antidepressants may also provide this benefit by increasing PRL levels [117]. The drug famotidine (H2 blocker) has been shown to provide symptomatic relief in COVID-19 patients, and H2 blockers also have a positive effect on blood PRL levels [117,118]. In conclusion, multicenter clinical trials should be conducted in patients with COVID-19 to investigate the prognostic significance of immunomodulation with dopamine antagonists (domperidone/metoclopramide) in this disease. Dopamine antagonists can be used prophylactically and contribute significantly to the research findings [8].

10. Future perspectives and conclusion

PRL is a hormone with both proinflammatory and anti-inflammatory effects. High levels of PRL may have a protective effect at COVID-19. PRL may exacerbate disease by stimulating the release of some important cytokines. Elevated PRL level may worsen the prognosis of COVID-19 due to activation of cytotoxicity, production of proinflammatory cytokines (such as MIP-1 and IP-10), and suppression of Treg cells. For these reasons, it may exacerbate ARDS. However, PRL can inhibit hyperinflation in COVID-19 infections through its anti-inflammatory effects. Because of these anti-inflammatory effects, the potential of PRL to be a protective protein in viral diseases is an important property of PRL. Dopamine antagonists can increase the production of the immunostimulant PRL in COVID-19, thereby positively affecting immune activity. PRL can also reduce the inflammatory response by stimulating the production of progesterone, which has an immunosuppressive effect.

CRediT authorship contribution statement

Yousef Rasmi: Writing – original draft, Writing – review & editing, Resources. **Ladan Jalali:** Writing – original draft, Writing – review & editing, Conceptualization, Supervision, Resources, Visualization. **Saliha Khalid:** Writing – original draft, Writing – review & editing. **Ameneh Shokati:** Writing – original draft, Writing – review & editing. **Poonam Tyagi:** Writing – original draft, Writing – review & editing. **Alpaslan Ozturk:** Writing – original draft, Writing – review & editing. **Amir Nasimfar:** Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

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