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COVID–19 and Progesterone: Part 2. Unraveling High Severity, Immunity Patterns, Immunity grading, Progesterone and its potential clinical use.

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ABSTRACT

Severely ill COVID–19 (Corona Virus Disease of 2019) patients have a hyperinflammatory condition with a high concentration of pro-inflammatory cytokines termed the cytokine storm. This milieu is reported to cause acute lung injury, oxygen deprivation, multiorgan damage, critical illness, and often death. Post SARS–CoV–2 (Severe Acute Respiratory Syndrome Coronavirus 2) infection, the fight between the invading virus and the host's immune system would either terminate in recovery, with eradication of the infection and regulation of the immune system; or there would be a continuation of immune attacks even after the virus has been cleared, leading to immune dysregulation and disease. This outcome is chiefly dependent on two factors: (1) the patient's immune response, and (2) sufficiency plus efficiency of the regulator(s). Concerning the first, the present research introduces a framework based on different types of immune responses to SARS–CoV–2 along with known disease examples, and how this relates to varying clinical outcomes and treatment needs for COVID–19 patients. About the second factor of 'regulator(s)', part 1 of the manuscript described in depth the regulatory role of progesterone in COVID–19. The present study investigates five immunity patterns and the status of the regulatory hormone progesterone with respect to the two established demographic risk factors for COVID–19 high-severity: male sex, and old age. The study evaluates the status of progesterone as a credible determinant of immune regulation and dysregulation. It duly relates the immunity patterns to clinical outcomes and evinces indications for clinical use of progesterone in COVID–19. It proposes a clear answer to the question: "why are males and old patients most likely to have critical illness due to COVID–19?" The study highlights clinical domains for the use of progesterone in COVID–19. Part 2 of this research introduces the concept of immunity patterns and immunity grading. These concepts herewith provided for the clinical course of COVID–19 also apply to other hyperinflammatory conditions. Possible clinical applications of progesterone to treat critically ill COVID–19 patients will open an avenue for hormonal treatments of infections and other immune-related diseases.

1. Introduction

COVID-19 is an infectious disease characterized by varied scale, type and duration of adaptive immune responses to the SARS-CoV-2. The immune system is a chief determinant of pathogenesis due to SARS–CoV–2 infection. When SARS-CoV-2 bypasses innate immune defenses, the adaptive immune system gets activated. It has two subdivisions: cell–mediated immunity T helper (Th) cells type 1 (Th1) and humoral immunity T helper (Th) cells type 2 (Th2). Cell-mediated immune responses involve destruction of SARS-CoV-2 infected cells by cytotoxic T cells and destruction of intracellular pathogens by Th1 cells. Th1 cells release pro-inflammatory cytokines inducing intracellular killing of SARS-CoV-2. Th1 cells also contribute to humoral immunity by inducing the production of opsonizing antibodies. Th2 cells initiate the humoral response by activating naive B cells to secrete IgM and induces the production of other antibody isotypes. These specific antibodies help with opsonization, activation of the complement pathway, and phagocytosis of the SARS-CoV-2. Th2 cells resolve cell-mediated inflammation by secreting anti-inflammatory cytokines and regulating the Th1. Th1 and Th2 regulation are important for clearing SARS-CoV-2 infection and recovery from COVID-19 (Berger, 2000). A SARS-CoV-2 infected individual's ability to achieve this regulation depends on three factors: viral load, immunity, and regulatory mechanisms. Part 1 of the manuscript is about the regulatory functions of progesterone. This part 2 investigates the role of individual immunity in COVID-19.

2. Methods

The present concept-based theoretical investigative research work was carried out in the city of Mumbai, Maharashtra, India from April 1,

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2020 to December 31, 2020 based on the following stepwise methodology protocol.

The foundation of present research is the concept of immunity patterns. Different types of immunity patterns are outlined. This is followed by the presentation of disease conditions which are clinically well established examples representing each of the five different immunity patterns. This is followed up by establishing the roles of these immunity patterns for COVID-19 outcomes. The clinically supported concept of the immunity patterns and status of the regulator progesterone was evaluated in the COVID-19 high severity and low severity groups. To this end, the immunity grading method was established and introduced to investigate and explain the varying severity of COVID-19 in different age-sex groups.

Formative research questions based theoretical investigations were carried out to find other biological factors that could affect progesterone levels and immunity patterns. This was a widely open question. The first step was to research for parameters that relate to high mortality in COVID-19; followed by evaluation of these parameters with respect to cell mediated immunity and progesterone. For example, one such parameter found was Vitamin D. For this factor research questions were (1) does Vitamin D relate to cell-mediated immunity? (2) does vitamin D relate to progesterone? (3) is there a connection among vitamin D, cell mediated immunity and progesterone? (4) what would be the outcome of these factors on immunity grading? Similarly the effect of other high risk factors on COVID-19 outcomes was probed, attending to severity parameters irrespective of age or sex. Enlisting of these factors was done to provide a detailed checklist of severity parameters for COVID-19. All illustrations and tables are originally prepared.

3. Results And Discussion

3.1. (A) Immunity patterns

In vivo, broadly there are three possible scenarios when cross-regulation of cell-mediated and humoral immunity is active after challenge by an infectious agent: (1) Th1 and Th2 in balance, (2) low Th1 with raised Th2, and (3) raised Th1 with low Th2. When cross-regulation of cell-mediated and humoral immunity is inactive, one more immunity pattern is possible (4) raised Th1 and raised Th2 (Fig. 1). A fifth immunity pattern is immunodeficiency or immunosuppression. At the time of infection an individual may have any one of these immunity patterns to varying extents. The symptoms of disease depend on the kind of infection and replication of the infectious agent and the immune response pattern. Immune responses to SARS–CoV–2 are different in patients with severe and non–severe course (Shi et al., 2020).

3.1.1. Immunity pattern 1: Th1 and Th2 in balance

Th1/Th2 cells in a balanced state (Fig. 1A) mount a moderate immune response taking moderate time for incubation as well as Th1/Th2 homeostasis. The incubation period is defined as the time between exposure to the pathogen and onset of signs and/or symptoms of clinically apparent disease. Asymptomatic patients have lower viral load (Zhou et al., 2020). COVID–19 patients with balanced Th1/Th2 typically are asymptomatic or present with mild symptoms depending on the viral load (Chan et al., 2021).

3.1.2. Immunity pattern 2: Th1 low with Th2 high

Low Th1 with raised Th2 (Fig. 1B) is a suboptimal immunity status for killing the intracellular virus; and the clinical outcome of SARS–CoV–2 infection would depend on whether the patient's immune system is competent or impaired. In patients with lasting impairment of Th1 immunity post–infection, it would lead to an inability to clear the infection, the possibility of viral reactivations, and secondary infections because cell-mediated immunity is crucial for attacking the intracellular infection and more specifically for killing virus-infected cells (Jiang et al., 2020).

With respect to SARS–CoV–2, Jiang et al. (Amodio et al., 2020) and Amodio et al. (Fishman and Perelson, 1999) both noted that a longer incubation time may lead to a high rate of asymptomatic and sub–clinical infection among immunocompetent individuals. In immunocompetent patients, depending on the rising viral load and parallel induction of Th1 immunity, the patient may exhibit symptoms ranging from none to mild or moderate, as the infection and hence the disease progresses over a long incubation period. Depending upon the viral load, patients who initially had a low Th1 response could mount a stronger cell-mediated immune response later and more slowly. Interestingly, their start with low Th1 and high Th2 is an advantage, with better prospects for Th1/Th2 homeostasis. This is because when Th1 is initially low and then increases, Th2 which is initially high gets cross-regulated (Xue et al., 2019). After the rise of cell-mediated Th1 immunity, when the infection gets defeated and starts to clear, there would be the need for humoral Th2 immunity and regulatory mechanisms to normalize the elevated Th1 response. Thus higher Th2 humoral immunity initially, topped up with post-infection specific humoral immunity, is beneficial for recovery in COVID-19 patients with intact cross-regulation.

Disease example: Atopic diseases have Th2 predominance (Akdis et al., 2003). Lower ACE2 expression in the nasal epithelial cells of asthma and allergic rhinitis patients is reported as compared to healthy individuals (Kimura et al., 2020). A large, 2–site cohort study of patients positive for COVID–19 confirmed that atopy is significantly associated with less severe COVID–19 outcomes. It reports that the presence of atopy could be predictive of a decreased need for hospitalization for COVID–19 (Keswani et al., 2020). Atopic status protects against the most severe, often fatal consequences of SARS-CoV-2 infection. The protective effect of atopic status against severe lung disease has been found to be evident throughout all age subsets in a mixed study group of atopic females and males (Scala et al., 2020).

3.1.3. Immunity pattern 3. Th1 high with Th2 low

It has been proposed that an exception to the inverse relationship between incubation period and severity of the disease is unlikely for SARS–CoV–2 (Kaslow, 2020). An inverse correlation between the length of the incubation period and the severity of the disease is reported for other coronaviruses (Virlogeux et al., 2015). Th1 dominance (Fig. 1C) contributes to the excessive inflammatory response and cytokine storm with tissue damage and organ injury along with the production of loads of debris from this protective yet destructive immune attack (Guihot et al., 2020). Further, SARS–CoV–2 acts on T cells with its superantigen (Cheng et al., 2020). Compared to a normal antigen-induced T-cell response where 0.0001–0.001% of the body's T-cells are activated, these superantigens are capable of activating up to 20% of the body's T-cells (Li et al., 1999). Activation of large numbers of T cells induced by the SARS–CoV–2 superantigens adds to the host–Th1 dominance (Yomogida et al., 2013), and results in a massive release of cytokines and uncontrolled tissue damage, organ injury, and toxic shock (Faulkner et al., 2005).

In this situation the immune system, which had elevated Th1 prior to the infection, gets its Th1 manifold raised even more while responding to the SARS–CoV–2 infection. This accelerates and magnifies the cytokine storm and is considered the root cause of pathogenic inflammation in COVID–19 (Ouyang et al., 2020, Qin et al., 2020, Sun et al., 2020). These patients would have severe symptoms with a short incubation period either from the time of exposure to the virus or from the time of noticing the first symptoms. Plus, they would take a long time to achieve Th1/Th2 homeostasis post infection as Th1, which was already raised, is further amplified and so there will be poor and delayed cross-regulation of Th2. Hence, if patients with raised Th1 immunity get infected by SARS–CoV–2, they would be at risk of suffering critical COVID–19 illness. In some of these patients uncontrolled Th1 immune dysregulation may deteriorate their condition rapidly and prove fatal (Cron, 2020).

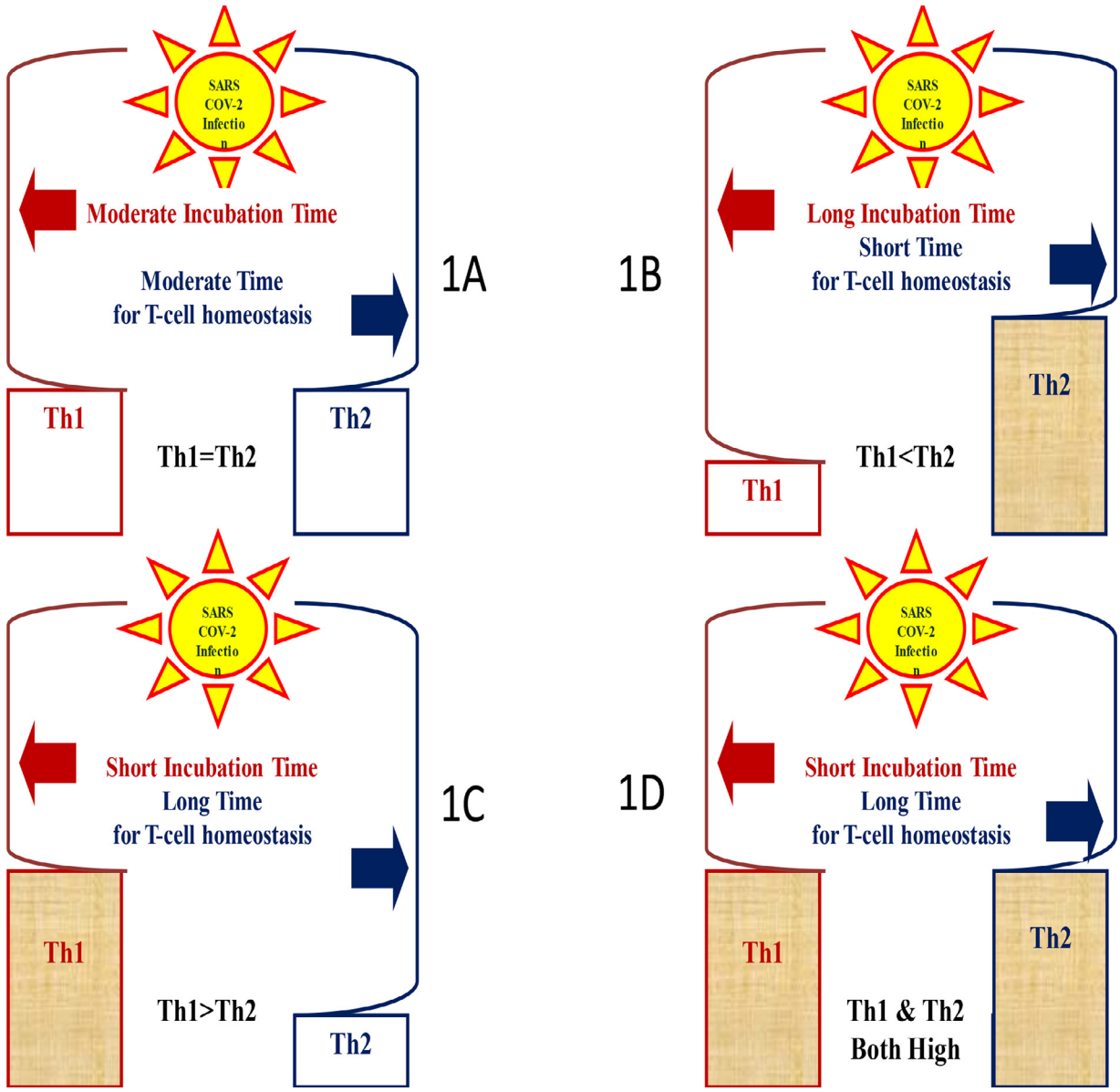

Fig. 1. Schematic illustration: Immunity patterns.

Disease example: Favalli EG et al (Favalli et al., 2020) describes COVID–19 and rheumatoid arthritis as two very different diseases which are nevertheless very close. This is because their pathogenesis shares excessive and self–damaging Th1 and Th17 cytokine secreting immune responses. When these two diseases meet, there is a further enhancement of cytokine secretions, inflammation and organ injuries. Patients with rheumatic disease and COVID–19 infection are reported to be more likely to require mechanical ventilation (D'Silva et al., 2020). It is for this similarity in pathophysiology that anti–inflammatory treatments, mostly used in rheumatology, are considered for COVID–19 (Haberman et al., 2020).

3.1.4. *Verification of mutually reciprocal Th1/Th2 paradigm*

Remarkably, the occurrence of rheumatoid arthritis in atopic patients is found to reduce the atopy symptoms by 40 to 50% affirming that regulation of Th1 and Th2 cells strongly influences the inflammatory responses and disease outcome (vanRoon and Bijlsma, 2002). The observations about the above discussed two diseases, rheumatoid arthritis (Th1 predominance) and atopy (Th2 predominance), verify the above concept of immunity patterns for COVID–19. Further, infections are a common comorbidity in long-term atopic dermatitis (Bekic et al., 2020). Patients suffering from chronic atopic dermatitis show increase in Th1. Th1/Th2 balance can vary during the chronic phase of atopic dermatitis (Su et al., 2017).

3.1.5. *Immunity pattern 4: Th1 high with Th2 high*

When the immune regulatory mechanisms fail, cell-mediated and humoral immunity do not cross-regulate each other effectively, resulting in immune disruption with both Th1 and Th2 being high (Fig. 1D) (Crimeen-Irwin et al., 2005). Earlier in this section, based on the immunity pattern concept for immunity pattern 2 (Th1 low and Th2 high) and immunity pattern 3 (Th1 high and Th2 low), the benefits of high Th2 and the risks of high Th1 for COVID-19 are explained in detail. In immunity pattern 4 with Th1 as well as Th2 high, the risk of high Th1 is applicable although Th2 is also raised due to pre-existing failure of cross-regulation. Patients with this immunity pattern are most likely to present severe symptoms with a short incubation period either from the time of exposure to the virus or from the time of noticing the first symptoms. Plus, they would take a long time to achieve Th1/Th2 homeostasis post infection as Th1, which was already raised, is further amplified

plus immune regulation and cross-regulation by Th2 both are unavailable. Hence, patients with immunity pattern 4 could get more critically ill than those with immunity pattern 3. In these patients, in absence of timely intervention with immune regulatory therapy, uncontrolled Th1 immune dysregulation may deteriorate their condition rapidly and prove fatal (Cron, 2020).

Disease example: Metabolic syndrome is a cluster of metabolic abnormalities associated with obesity, insulin resistance, dyslipidemia, and hypertension in which inflammation plays an important role. There is upregulation of both Th1 and Th2 cytokines in metabolic syndrome (Surendar et al., 2011). Patients with metabolic disorders like obesity, diabetes, cardiovascular and liver disease may face a higher risk of SARS-CoV-2 infection and COVID-19. These disorders greatly affect the course and prognosis of COVID-19 and are associated with significantly worse COVID-19 outcomes (Costa et al., 2020). A meta-analysis of main predictors of COVID-19 associated mortality rate in hospitalized patients found that diabetes mellitus is the best predictor of mortality rate in an age- and sex-dependent manner (Corona et al., 2021). Metabolic stress can cause pathologic activation of the immune system. Therefore, metabolic disorders including diabetes mellitus can manifest and progress as an inflammatory disorder, with inflammation producing severe consequences (Hameed et al., 2015). SARS-CoV-2 induced activation of the immune system could further aggravate these pre-existing inflammatory conditions.

3.1.6. Immunodeficiencies or immunosuppression

Immunocompromised patients, including those with inborn errors of immunity, may be at increased risk for severe or prolonged infections with SARS-CoV-2 (Kinoshita et al., 2021).

Cancer and organ transplant patients are immunocompromised chiefly due to treatment. Compared to the general population, adult cancer and organ transplant patients with COVID-19 are found to suffer higher comorbidities, have higher levels of inflammatory markers at diagnosis, and higher rates of intensive care and hospital mortality (Belsky et al., 2021).

Inborn errors of immunity are genetic disorders with broad clinical manifestations, ranging from increased susceptibility to infections to significant immune dysregulation (Delmonte et al., 2019). Primary immunodeficiency disorder (PID) refers to a large heterogeneous group of disorders that result from defects in immune system development and/or function. PIDs are broadly classified as disorders of adaptive immunity (i.e., T cell, B-cell or combined immunodeficiencies) or of innate immunity (e.g., phagocyte and complement disorders). Although the clinical manifestations of PIDs are highly variable, many disorders involve an increased susceptibility to infection. (McCusker et al., 2018).

Young patients with primary immunodeficiency have a prevalence of Th2 but as they get older, due to alarmins, this balance can change to Th1 prevalence (Joshua, 2020, Yang et al., 2017). Compared to the general population, adult patients with PID and symptomatic secondary immunodeficiency display grater morbidity and mortality from COVID-19 (Shields et al., 2021).

Here it is important to mention that some orphan hereditary diseases present immunodeficiencies and hormone deregulation. For example, beta thalassemias are a group of hereditary blood disorders characterized by anomalies in the synthesis of the beta chains of hemoglobin resulting in variable phenotypes ranging from severe anemia to clinically asymptomatic individuals. Total annual incidence of symptomatic individuals is estimated at 1 in 100,000 throughout the world and 1 in 10,000 people in the European Union (Galanello and Origa, 2010). Immune competence is affected in beta-thalassemia and involves numerous quantitative and functional defects, involving T and B lymphocytes, immunoglobulin production, neutrophils and macrophages, chemotaxis and phagocytosis, as well as the complement system (Farmakis et al., 2003). Iron excess may derange the immune balance in favor of the growth of infectious organism and the accumulation of iron in different organs leads to different clinical complications of iron overload. The anterior pituitary is particularly sensitive to iron overload which disrupts hormonal secretion resulting in hypogonadism (Toumba et al., 2007).

In part 1 of the manuscript the regulatory role of progesterone for COVID–19 was corroborated. To further substantiate applicability of both these parameters, immunity patterns and progesterone, it will be appropriate to appraise their status for the established COVID–19 high-severity groups.

3.2. (B) Immunity patterns and progesterone status in COVID–19 high severity groups

Two established high severity groups for COVID–19 are old age and male sex. Based on these two factors, it would be pertinent to explore (I) Effects of old age on the regulator progesterone, (II) Effects of old age on the immunity patterns, (III) Sex and levels of the regulator progesterone, (IV) Sex, immunity patterns and old age, and (V) Comprehensive presentation and immunity grading of the four age–sex groups: old males, young males, old females and young females, with respect to immunity patterns, status of the regulator progesterone, and different COVID–19 severity.

3.2.1. (I) Effect of old age on the regulator progesterone

Progesterone decreases significantly with age in both men and women (Genazzani et al., 1998). Ageing, hormones and immunity are interconnected (Horstman et al., 2012).

3.2.2. (II) Effect of old age on the immunity patterns

The respiratory system undergoes various hormonal, anatomical, physiological and immunological changes with age. Reduced levels of progesterone and estrogen could cause decreased muscular strength, decreased relaxation of bronchial smooth muscle, and increased compression of thoracic spine due to osteoporosis (Memoalia J Anjum et al., 2018). Age significantly determines the clinical features and prognosis of COVID–19. Elderly patients with COVID–19 are found to be more likely to progress to severe disease. Acute respiratory distress as graded by the Pneumonia Severity Index is higher in elderly than in young and middle-aged COVID–19 patients. Prognosis is worse in patients older than 60 years. Hospitalization, ICU admissions, and death increase with age. Mortality is higher in elderly than in young and middle–aged patients (Liu et al., 2020, Liu et al., 2020, Koff and Williams, 2020, CDC COVID-19 response team 2020).

There are three main findings about effects of ageing on the T-cells.

(1) Immunosenescence:

Immunosenescence refers to the gradual deterioration of the immune system brought on by advancing age (Pangrazzi and Weinberger, 2020). Ferrando–Martínez S et al (Ferrando–Martínez et al., 2011) reported that an important cause of elderly impaired responses to newly encountered pathogens is an age–related deregulation of T cell homeostasis and accumulation of age-associated defects in naive T cells.

(2) Defects in antiviral T cell responses and T cell regulation:

MicroRNAs are single–stranded RNAs which are differentially expressed in viral acute respiratory infections and they can be responsible for high morbidity and mortality due to such infections (Leon-Icaza et al., 2019). In old age, there is reduced microRNA–181a expression in T cells, which contributes to defective anti-viral T cell responses; and there is increased production of microRNA–21 which favors Th1 effector cell generation (Kim et al., 2019). Holcar M et al (Holcar et al., 2015) have demonstrated a decrease in the percentage of total Tregulator cells and an increase in the percentage of total Teffector cells with age, and a consequent immense increase in the Teffector/Tregulator ratio.

(3) Increase in Th1:

Aging is associated with increases in levels of circulating cytokines and pro-inflammatory markers; this phenomenon is called "inflamm–aging" (Michaud et al., 2013). The microenvironment in which T helper cells develop in older people may cause production of more cells committed to Th1 type cells than that in younger subjects. On analysis of the effect of ageing on the responsiveness of human T helper cells to polyclonal stimuli, Sakata–Kaneko S et al (Sakata–Kaneko et al., 2000) discovered that at the time of antigenic stimulation with subsequent induction of lymphokine secretion and cell adhesion molecule expression, the T helper subset in the peripheral blood of aged individuals is found to contain a greater proportion of cells committed to Th1 type cells than that from young individuals (Sakata–Kaneko et al., 2000). These T cell related changes could contribute to dysregulated and damaging immune responses to SARS–CoV–2 in the elderly.

3.2.3. (III) Sex and levels of the regulator progesterone

Men have lower levels of progesterone than women. Young men have lower levels of progesterone than young premenopausal women. This low level further decreases with age. Zumoff et al (Zumoff et al., 1990) reported a serum progesterone (0.18±0.03 ng/mL) in healthy men aged 37–51 years that is approximately one–fourth of the serum progesterone levels demonstrated by Muneyyirci–Delale et al (Muneyyirci–Delale et al., 1999) in healthy young men aged 24–35 years (0.78 ± 0.28 ng/mL).The latter was similar to levels in young women aged 24–35 years in the follicular phase of the menstrual cycle (0.68 ± 0.34 ng/mL) but was a fraction of these young women's in the mid-luteal phase of the menstrual cycle (reference range 12-32ng/mL) (Wood et al., 1985). The reference range for progesterone levels in adult men is 0.13–0.97 ng/mL (Burtis and Ashwood, 1999), which clearly encompasses the levels found in both groups of men. After menopause, progesterone diminishes to about 0.26± 0.18ng/mL (Michaud et al., 2013). Declining sex hormones in both men (andropause) and women (menopause) are associated with dysregulation of the immune system (Gomez et al., 2019).

3.2.4. (IV) Sex, immunity patterns and old age

While the age-related fundaments about raised Th1 and low progesterone are valid for both men and women, COVID–19 do not affect them equally. Male patients have higher COVID–19 mortality than females (Jin et al., 2020). Data collated by Global Health 50/50 shows that in the vast majority of countries where data is available, men are consistently dying at a higher rate than women (Global Health 50/50 the sex 2020). In a mega study involving a large number of critically ill COVID–19 patients admitted to ICUs of 72 Italian hospitals, the majority were older men. A large proportion of them required mechanical ventilation and high levels of positive end expiratory pressure, and ICU mortality was 26% (Grasselli et al., 2020). The difference in the death rate by COVID–19 between women and men decreases with age, but the death rate remains lower in females than in males. Setting men's COVID-19 death rate equal to 100%, women's death rate is only 27.8% (−72.2%) at ages 2 to 59 years, and 50.6% (−49.4%) at ages 60 to 89 years (Cagnacci and Xholli, 2020).

Changes in sex steroids impact regulation of the Th1 and Th2 immune responses in old age, with implications for severe and fatal outcomes of infections (Hall and Klein, 2017). It is found that women present strongerTh2 immunity (Desai and Brinton, 2019) and men have stronger Th1 immunity (Abdullah et al., 2012). In healthy men and women, the polarization of immune response into Th1/Th2 cytokines or T helper cell subsets is flexible. The ratio of these cells swiftly varies according to physiological demands and clinical conditions. Aging is associated with a loss of this flexibility due to alterations in the levels of sex hormones (Ardia et al., 2011). Yet even though both sexes have declining sex hormones with ageing and increase in Th1 immunity, men and women have different COVID–19 outcomes. This is chiefly because increases of Th1 due to ageing, immunosenescence and hormonal changes do not affect the Th2 mediated humoral immune response. Tajima K et al. (Tajima et al., 2011) have proved that the levels of Th1–type cytokines in the bronchoalveolar lavage fluid of ovariectomized rats were significantly higher than those in sham rats, while the levels of Th2–type cytokines in both bronchoalveolar lavage fluid and serum were comparable between ovariectomized and sham rats.

These findings suggest that in the aged, though the immune responses would be in a Th1–polarized manner while levels of sex hormones are declining, the basic humoral immune status is unchanged. This is more favorable for aged women than men suffering from COVID–19 because women, in general, have Th2 predominance which remains unaffected; while men, in general, have low Th2 which also remains unchanged. In consequence, aged women have higher Th2 than aged men. When equal numbers of severe COVID–19 female patients (average age 63.1 years) and severe COVID–19 male patients (average age 59.4 years) were analyzed for the concentration of serum SARS–CoV–2 IgG antibodies, the female patients had higher concentrations of serum SARS–CoV–2 IgG antibody than the male patients. This indicates that even after the age-related immunosenescence and increase in Th1, old-women have better humoral immunity than old men to SARS–CoV–2 (Zeng et al., 2020). Thus, despite similar age-related changes with increased Th1 and low progesterone in both males and females, the general difference in Th1 and Th2 predominance means that chances of recovery from COVID–19 are higher in elderly women than in elderly men due to their stronger humoral immunity and antibody production. This is also evident from the better efficacy of vaccines in older women than in older men. For example, when vaccine efficacy against influenza was measured using the hemagglutination inhibition assay, the antibody response titers were higher in women than in men at all ages. The higher antibody titers of older women were found to be associated with lower hospitalization and mortality rates compared to aged men (Aurwein–Teissl et al., 2002, Cook, 2008).

3.2.5. (V) Comprehensive presentation of the age–sex groups with the immunity patterns, the regulator progesterone, immunity grading and different COVID–19 severity

COVID–19 severity and mortality, from highest to lowest, are graded by age and sex as indicated in Table I: Old men> Old women > Young men > Young women.

Old males: In aged men infected with SARS–CoV–2, there would be three stages of Th1 escalation: (1) Generally pre-existing Th1 predominance in men (2) Rise in Th1 due to ageing with no cross-regulation of Th2 due to Immunosenescence and hence, the low Th2 status continues (Fig. 2), and (3) Activation of the cell-mediated Th1 immune response to SARS–CoV–2 infection (Table 1). This excessive Th1 activity with low Th2 would cause cytokine storm, tissue injury, organ damage, and severe disease with poor outcomes. It may prove fatal due to low levels of the regulator progesterone (inadequate regulatory actions), low Th2 (poor humoral immunity), and uncontrolled immune dysregulation.

Old females: Like old males, in old females too there would be age-related Th1 increase, but since in general women have Th2 orientation, there are only two stages of Th1 escalation in COVID–19 suffering older women: (1) Rise in Th1 immunity due to ageing, and (2) Activation of the cell-mediated Th1 immune response to SARS–CoV–2 infection (Table 1). This can lead to excessive Th1 activity with cytokine storm, tissue injury, organ damage, and severe disease. Menopause is an independent risk factor for female COVID–19 patients (Ding et al., 2020). Even though at higher risk of immune dysregulation than younger women, aged postmenopausal COVID–19 women with low progesterone levels are presenting with less critical illness and are dying less of COVID–19 than equally old COVID–19 male patients. This is due to their lower baseline activity of Th1 than in the aged COVID–19 male patients, and higher Th2 humoral immunity, which neutralizes extracellular virus particles, thereby lessening the stimulation of Th1 cell-mediated immunity. Like old men, old women too have low progesterone levels and rise in Th1 due to ageing with missing

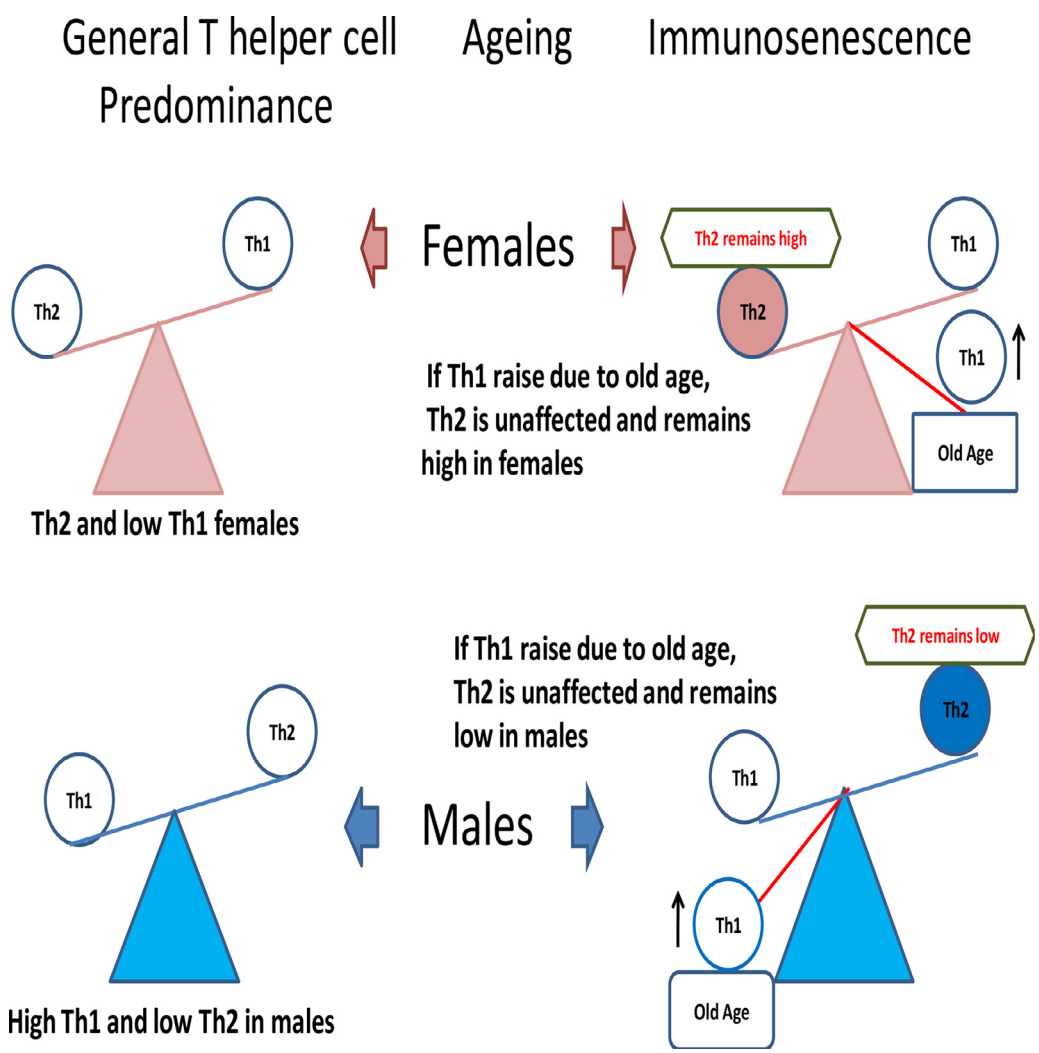

Fig. 2. Effect of old age and immunosenescence on female and male T helper cell immunity.

Table 1
Age–Sex groups, Stages of Th1 escalation, Progesterone levels and COVID–19 severity.

Age–Sex Group	Generally Predominant T-cell Immunity	Old Age T-cell Immunosenes-cence	SARS–CoV–2 Infection & T-cell Activation	Sum of Th1 Escalation Stages	Progesterone Levels Hierarchy	COVID–19 Severity Hierarchy
Young females	Th2	–	Th1	One	High	Low
Young Males	Th1	–	Th1	Two	Low	High
Old females	Th2	Th1	Th1	Two	Lower	Higher
Old Males	Th1	Th1	Th1	Three	Lowest	Highest

cross-regulation of Th2. Hence, Th2 is unaffected and continues to be high (Fig. 2). Their risk of severe illness and mortality is lower than old men but higher than that of young males. They both have two stages of Th1 escalation, but young men have higher progesterone than aged postmenopausal women (Zumoff et al., 1990, Muneyyirci–Delale et al., 1999).

Young males: In young men infected with SARS–CoV–2, the rise in Th1 due to old age is not there. Hence, there would be two stages of Th1 escalation: (1) Generally preexisting Th1 predomination in men and (2) Activation of cell-mediated Th1 immune response to SARS–CoV–2 infection. The young males have less severity and mortality due to COVID–19 than old males (Table 1). Their progesterone levels are low but higher than those of aged men (Zumoff et al., 1990, Muneyyirci–Delale et al., 1999); and they have one less stage of Th1 escalation. Although as explained further the young males have higher severity than young females.

Young females: In young females infected with SARS–CoV–2, generally there is Th2 predominance and the rise in Th1 due to old age is not there. Hence, there would be only one stage of Th1 escalation: which is activation of the cell-mediated Th1 immune response to SARS–CoV–2 infection (Table 1). Plus, they also have higher levels of the regulator progesterone, and theoretically optimum chances of immune regulation. Initially there would be cross-regulation of Th2 followed by development of specific humoral immunity, immune homeostasis, and recovery. Thus young females have less severe illness than the other age-sex combinations.

The above evidence about low progesterone and raised Th1 in the high-severity groups substantiates and confirms applicability of the con-

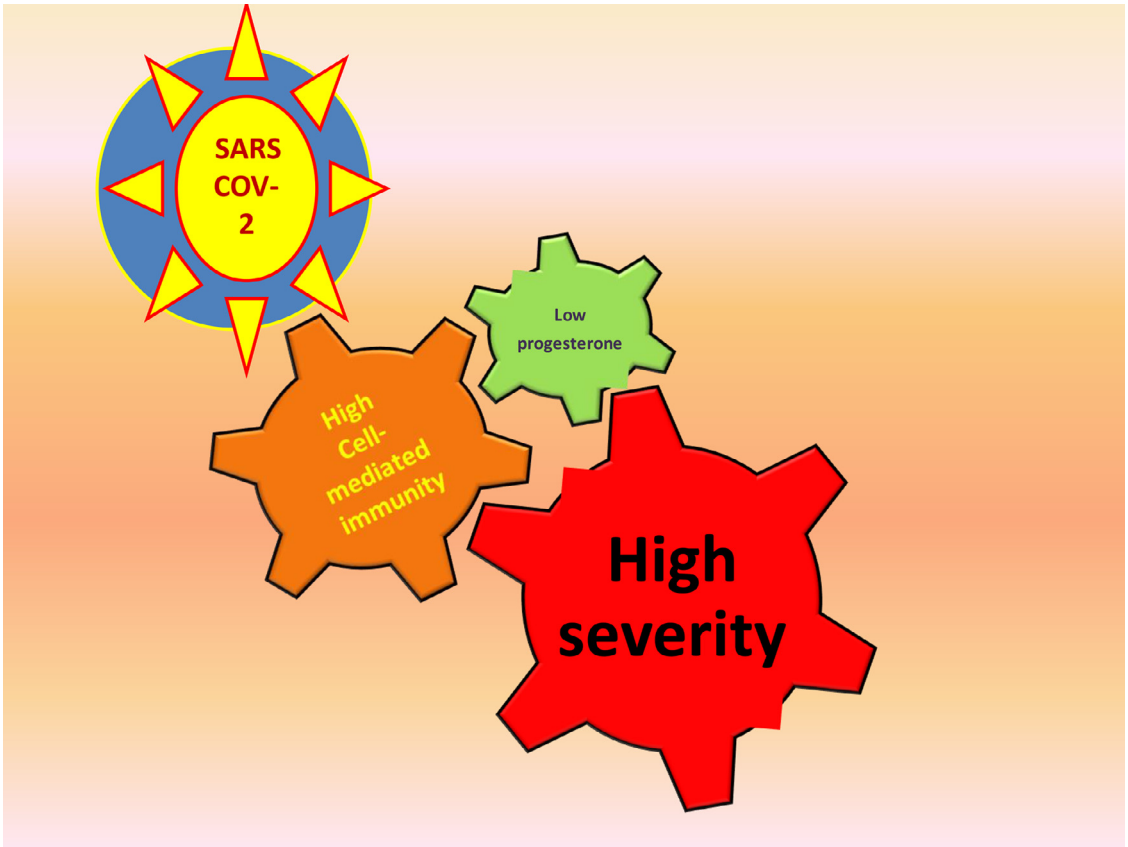

Fig. 3. Schematic illustration. SARS–CoV–2 infection in a patient with high Th1 and low progesterone link to severe COVID-19.

Table IIA
Factors affecting Progesterone and Th1.

Factor	Finding	Directly affects	Reported mortality
Age	Old	Progesterone and Th1	High
Sex	Male	Progesterone and Th1	High
Hypoxia	Critical	Progesterone	High
Cholesterol	Low	Progesterone	High
Vitamin D	Low	Th1 More if Progesterone is low	High
Comorbidities	Th1 comorbidities	Th1	High
Reproductive status/ surgeries	Menopause or gonadectomy	Progesterone and Th1	High

Table IIB
Check-list of factors for patients to predict likely severity with a model example.

Factor	Parameter	Status	Severity Score
Age	Old	Yes	1
Sex	Male	No	0
Hypoxia	Critical	No	0
Cholesterol	Low	Yes	1
Vitamin D	Low	Yes	1
Comorbidities	Th1 comorbidities	Yes	1
	Hypertension	No	0
	Cardiac disease	No	0
	Kidney disease	Yes	1
Reproductive status/ surgeries	Menopause or Gonadectomy	Yes	1
		Total Score	**6**

Score: Yes for any parameter = 1
Score: No for any parameter = 0
Interpretation: Higher the total score higher the possibility of COVID-19 severity.

cept of immunity patterns and their regulator progesterone for COVID–19. The evidence indicates that high Th1 with decreased progesterone could lead to severe COVID–19 outcomes, and high risk of mortality (Fig. 3).

3.3. (C) Factors related to progesterone and cell-mediated immunity

While old age and male sex are the chief known risk factors for severe disease, there are other factors affecting progesterone and cell mediated immunity and hence immune regulation, and COVID–19 outcomes irrespective of age and sex. Table IIA enlists the factors affecting progesterone and/or cell-mediated immunity along with their reported COVID-19 mortality. Table IIB suggests the same list of factors as a check-list for possible risk of severity in COVID-19 patients.

3.3.1. Oxidative stress

Oxidative stress is associated with changes found in COVID–19 patients. It participates in the cytokine storm, coagulopathy, and cell hypoxia (Cecchini and Cecchini, 2020). Hypoxia results in decreased ATP synthesis and increased formation of reactive oxygen species while decreasing the activity of the normal cellular antioxidant system. The resulting oxidative stress initiates apoptosis, which contributes significantly to cell death observed in hypoxia (Wheaton and Chandel, 2011). Progesterone levels decrease in response to oxidative stress (Hayashi et al., 2003). Various mechanisms, including the decline of sex hormones,

link oxidative stress with ageing (Vitale et al., 2013). One of them is that the alveolar dead space increases with age, reducing arterial oxygen without impairing carbon dioxide elimination. Older adults have a diminished ventilatory response to hypoxia and hypercapnia (Sharma and Goodwin, 2006).

3.3.2. Cholesterol

Progesterone is produced from cholesterol. Cytochrome P450 converts cholesterol into pregnenolone, which gets further converted into progesterone. Hence low cholesterol would directly relate to low progesterone (Hu et al., 2010). Low cholesterol levels are associated with more severe disease in patients infected with SARS–CoV–2 (Peng et al., 2021). Secondly, hypoxia, which is common in COVID–19, decreases progesterone synthesis from cholesterol by attenuating cytochrome P450 production (Kuru et al., 2018, Nishimura et al., 2006).

3.3.3. Vitamin D

The two hormones progesterone and vitamin D cooperate with each other for sequential and effective regulation of the immune system. Vitamin D plays an important role in modulating the immune response to infections. There is an established association between vitamin D deficiency and an increased risk for infections, and vitamin deficiency is associated with poorer outcomes from infectious diseases (Watkins et al., 2015). Jain A et al (Jain et al., 2020) have measured vitamin D levels in patients suffering from COVID-19. They found that vitamin D level is markedly low in severe COVID-19 patients. They have also noted that serum levels of inflammatory markers are high in vitamin D deficient COVID-19 patients. Raharusun P et al (Raharusun et al., 2020) have reported that COVID–19 patients with vitamin D deficiency have an increased risk of mortality. This research concluded that a majority of the COVID–19 cases with insufficient and deficient vitamin D status died and the odds of death were highest in older male cases with a pre–existing condition and below-normal vitamin D level recorded and measured prior to COVID-19. Entrenas CM et al (Entrenas Castillo et al., 2020) reported that early vitamin D treatment of hospitalized COVID-19 patients significantly reduced severity of COVId-19 and intensive care unit admissions.

Connecting to the present study, both the immunity pattern concept and progesterone regulation can explain these associations of mortality with male sex and vitamin D deficiency. Thangamani S et al (Thangamani et al., 2015) have concluded that the progesterone and vitamin D nuclear hormone receptor ligands play important roles in regulating T cells. Progesterone is an inducer of the vitamin D receptor in T cells. This makes T cells highly sensitive to calcitriol, the active form of vitamin D. Increased expression of vitamin D receptors induced by progesterone allows highly sensitive regulation of T cells by vitamin D even when the vitamin D level is suboptimal. This regulatory pathway enhances the induction of regulatory T cells and suppresses Th1 cells. This results in effective regulation of T cells and helps to prevent adverse outcomes due to dysregulated immune responses. Males have low progesterone levels, and when their vitamin D is also deficient, it escalates the risk of an overshooting Th1 response, which can be described as the fourth stage of Th1 escalation (Kim, 2015).

3.3.4. Population-based variation

Average progesterone levels in women vary significantly at the inter–population and intra–population level as a function of age and acute metabolic energy status related to energy intake, energy expenditure, or a combination of both. In addition to effects of acute stressors, baseline progesterone levels differ among populations. The causes of such chronic differences are not well understood, but it has been hypothesized that they may result from varying tempos of growth and maturation and, by implication, from diverse environmental conditions encountered during childhood and adolescence (Núñez–de la et al., 2007).

3.4. (D) Potential clinical use of progesterone in COVID–19

Use of progesterone in clinical practice for non-endocrine and non-gynecological disorders is well established. Progesterone is used in treatment of inflammatory diseases with Th1 dominance.

Disease example: Rheumatoid arthritis patients suffer from Th1-driven autoimmune inflammation (Kosmaczewska et al., 2014, Schulze–Koops and Kalden, 2001). Disease activity of rheumatoid arthritis is characteristically regulated by hormones. Women with rheumatoid arthritis often go into remission during pregnancy (Szekeres–Bartho et al., 2001), and its outcomes get more severe with reproductive ageing. Women suffering from rheumatoid arthritis experience a slower physical decline before than after menopause (Mollard et al., 2018). Men older than 50 years suffering from rheumatoid arthritis have about twice the risk of osteoporosis compared to healthy controls (Kweon et al., 2018). Rheumatoid arthritis symptoms are related to changes in menstrual phases (Latman, 1983). Plasma progesterone levels in the luteal phase are significantly lower in women suffering from rheumatoid arthritis than in the control group (Valentino et al., 1993). Progesterone is therapeutically used to treat rheumatoid arthritis patients. Progesterone receptors are widespread in human cells including osteoblasts and osteoclasts (Spelsberg et al., 1999). Intra-articular administration of progesterone reduces inflammation in arthritic joints (Cuchacovich et al., 1988), repairs cartilage, and regulates remodeling of affected bones (Wardhana et al., 2013, Kini and Nandeesh, 2012).

3.4.1. Clinical target for COVID–19

As evident from the detailed research on the regulatory role of progesterone in both parts of this manuscript, progesterone could have therapeutic clinical applications for SARS–CoV–2 infection and COVID–19. Ideally,progesterone treatment of COVID–19 patients should be limited to treatment of the acute illness and recovery, irrespective of the patient's baseline plasma/serum levels of progesterone. It needs to be clearly understood that here the aim is to make best therapeutic use of the biological and regulatory effects of progesterone, and not hormone replacement therapy or corrections of hormones which is a different issue as well as a different application of the hormone.

3.4.2. Patient candidacy

As the majority of mildly or moderately symptomatic COVID–19 patients recover without complications of immune dysregulation, use of exogenous progesterone would be chiefly for those COVID–19 patients having severe symptoms with rapid worsening and critical illness related to immune dysregulation. As discussed before, the severely affected patients are highly likely to be low on progesterone with high Th1 immunity, in part due to their sex (males) or their age (aged men and postmenopausal women). Ding T et al (Michaud et al., 2013) have reported that progesterone levels in females with non-severe COVID-19 symptoms are higher [Median value 0.88 ng/mL (0.43–3.16)] than those of females with severe symptoms [0.36 ng/mL (0.27–1.45 ng/mL). So, measuring serum/plasma progesterone levels and Th1 cytokines panel levels, maybe done but is not mandatory when treatment needs to be started immediately or laboratory investigation cannot be done for lack of laboratory facilities or lack of time. Besides the patient's age and symptoms of COVID–19, case details about reproductive ageing, LMP (date of last menstrual period) for females, history of hormonal supplements, history of gynecological surgeries and co–morbidities with list of medications could be helpful. Overexpression of Th1 is more likely in those with a history of Th1-oriented comorbidity. Other indications of Th1 deviation include short COVID-19 incubation period from time of exposure to onset of symptoms; or disease progression after onset of first symptoms if the time of exposure to the infection is not known.

3.4.3. Laboratory investigations

If possible, measurement of serum/plasma progesterone level and Th1 cytokine panel levels will be useful for decision about the dose of

progesterone, records, and follow-up. It is important to understand that while in routine applications, the pretreatment value of serum/plasma progesterone is interpreted with reference to the laboratory's normal limits, for COVID–19 severely and critically ill patients the targeted physiological reference range would be that of young females in their mid-luteal phase (reference range 12-32 ng/mL) (Wood et al., 1985). Luteal phase is the Th1 regulating phase (Faas et al., 2000). CRP is a routinely used marker of inflammation and infection in clinical practice. Gursoy AY et al (Gursoy et al., 2015) have reported that the progesterone rise during the luteal phase might have a subtle effect on CRP, which is significantly lower in the luteal phase than in the follicular phase. Thus, as young premenopausal females suffer the least severity and mortalityfrom COVID–19, they provide an indication of the range of progesterone target levels for therapy. It would be ideal to refer to the normal limits reported by the local laboratory which have been established for the local population.

3.4.4. Phase of action

Careful monitoring of symptoms is important. Administration of progesterone would be most promising at an early stage, before the patient gets critically ill and before immune dysregulation has caused critical complications.

3.4.5. Drug

Physiological data and clinical outcomes demonstrate that bioidentical progesterone is more efficacious than its synthetic and animal-derived counterparts (Holtorf, 2009). It is important to note that micronized progesterone and pregnane derivatives are safe with respect to thrombosis, but not the norpregnane derivatives and Medroxyprogesterone acetate (Canonico et al., 2007). It is relevant to mention here that some synthetic progesterones are found to elevate alpha–1 antitrypsin concentrations in the blood. This could be protective as alpha–1 antitrypsin inhibits the TMPRSS2 involved in binding of SARS–CoV–2 to the host ACE2 (kishoreN Rizvi et al., 1978, Wewers et al., 1986).

3.4.6. Route and dose

The route of progesterone administration, dose, and duration of treatment would be the treating physician's decision based on the specifics of each case. The progesterone effect depends on concentration as well as infusion mode. It is important to note that "progesterone has dose dependent effects on hypoxia and neurotransmission, with low pulsatile doses having a positive effect whereas continuous and/or high doses may have negative effects (Hichri et al., 2012, Ramirez and Dluzen, 1987)". Unfer V et al (Unfer et al., 2006) conducted detailed work on the use of progesterone in clinical practice and evaluated its efficacy in diverse indications using different routes of administration. The distribution and concentration of the hormone in the tissues could vary depending on the route of administration, affecting therapeutic outcomes. A single 100mg dose of progesterone was given orally or as intramuscular injection to women during the follicular phase of two consecutive menstrual cycles: After oral administration serum levels of progesterone increased rapidly to reach luteal phase values within 1–4 hours; whereas following intramuscular injection too the progesterone levels increased rapidly but peaked 8 hours after administration to values 2.5 times higher than the luteal phase. Via both routes, the serum progesterone levels were found elevated for more than 12 hours (Ottoson et al., 1984).

Based on these findings, an appropriate dose for COVID–19 patients would be either 100 mg via the oral route or a lower dose for the intramuscular route to avoid the 2.5 times increment because the aim of administering the progesterone is regulation of the immune responses, not excessive suppression of the Th1 response. Massive Th1 suppression or Th2 deviation would be risky as it could camouflage the disease symptoms and provide favorable conditions for replication of any remaining SARS–CoV–2 virus or new infections.

For example, pregnant women have high progesterone levels which increase over the first to third trimesters (22.1 – 225 ng/mL) (Schock et al., 2016). Based on a systematic review and meta–analysis, Allotey J et al (Allotey et al., 2020) have reported that pregnant women with COVID–19 are less likely to manifest symptoms of fever and myalgia than non–pregnant women of reproductive age, although they might be at increased risk of complications and admission to an intensive care unit. This is similar to findings of pregnant women infected with swine flu. H1N1 pathogenesis is similar to SARS-CoV-2 with heightened Th1 immunity. A study has reported the presence of antibodies to progesterone in pregnant women suffering from swine flu. It was related to high levels of this hormone during pregnancy which could deviate the immune system excessively towards Th2**.** Maternal Th2 immune status is protective for the fetus in order to avoid abortion, but it could lead to formation of auto-antibodies due to Th2 deviation and diminished Th1 resulting in impaired ability to fight the virus (Shah et al., 2015).

3.4.7. Immunoregulation v/s immunosuppression

Irrespective of the cause of immune dysregulation in COVID-19: be it due to heavy viral load, pre-existing immunity pattern with raised Th1, suboptimal levels of progesterone or other regulatory factors, the logical antidote to immune dysregulation is immunoregulation and not immunosuppression. Immunosuppression with corticosteroids is used in COVID-19 patients mainly for suppressing the inflammation. Efficacy of corticosteroid treatment depends on the stage of COVID-19 (Bahl et al., 2021) and appropriate dose (Monreal et al., 2021). Administering it at an early stage of the SARS-CoV-2 infection in high doses is found to be harmful with excessive suppression of inflammatory responses leading to a virus-supporting milieu and also paving the way for mucormycosis (Veisi et al., 2021). Such clinical findings in some of the COVID-19 patients treated with corticosteoids indicate that an immune regulator like progesterone maybe a better option. Progesterone is one option to achieve optimal immunoregulation while avoiding excessive suppression of the Th1 response. Use of progesterone will also require clinical vigilance, especially about the right time of administration with regards to the stage of COVID-19 and appropriate dose.

Disease example: COVID-19 outcomes are found to be worse in those inflammatory arthritis patients who are on glucocorticoids than in those who are on anti-cytokine therapy (Tufan et al., 2020). About mucormycosis, most pathogenic fungi are intracellular infections and immunomodulating therapeutic agents that upregulate the immune response in the fight against fungal infections hold promise for enhancing the efficacy and safety of conventional antifungal therapy (Ademe, 2020). This is an indication that not immunosuppression but immunoregulation is the proper target to treat Th1 oriented COVID–19 patients with severe symptoms due to cytokine storm.

3.4.8. Duration

Suggested duration of treatment with progesterone for COVID–19 would be episodic, transient, only when needed, an emergency intervention to assist the patient to overcome the acute effects of immune dysregulation.

3.4.9. Caution

Blood pressure monitoring

Progesterone treatment significantly reduces resting mean arterial pressure although it increases plasma volume in humans (Barbagallo et al., 1995). There is no effect of progesterone treatment on adrenocorticotropic hormone, arginine vasopressin, renin, or heart rate responses to hypotension. It is suggested that a small increase in progesterone can reset resting mean arterial pressure and plasma volume, without altering reflex heart rate or endocrine responses to hypotension (Pecins–Thompson and Keller–Wood, 1997). Like other vasodilators it could be administered early to acute heart failure patients with normal or high blood pressure at presentation, but is best avoided in critical patients with low blood pressure (Metra et al., 2009).

3.4.10. Addendum

Two interesting addendums in regard to the immunity patterns:

First is the two-way effect of antibiotics. In patients with low Th1 and high Th2 immunity pattern, unless there is a bacterial infection present, antibiotics are best avoided to prevent lowering of the commensals and gut microbiota, as this could further lower the Th1 response and have a profound effect on the host immune system (Wu and Wu, 2012). For the same reason, the use of antibiotics could be therapeutic for patients with high Th1 and low Th2 immunity patterns as lowering the microbiota lowers Th1 and susceptibility to cytokine storm (Belkaid and Hand, 2014). Second, therapeutic drugs influence oxidative stress. It is interesting to note that the much-used drug hydroxychloroquine for COVID–19 downregulates oxidative stress (Liu et al., 2020), which is progesterone favoring condition. Remarkably, it substantiates the present research as it is actually reported to shift the excessive cell-mediated immune responses to Th2, in a dose-dependent manner (Ghasemnejad–Berenji and Ghaffari, 2018).

4. Conclusion

To conclude, the presented research indicates that recognizing the patient's immunity pattern and progesterone status is important for COVID–19. High Th1 and low progesterone predict severe outcomes of COVID–19. The study proposes reasons for the higher severity and mortality in males and the elderly. One stage lesser escalation of Th1 combined with higher Th2 is the most likely reason for less severity and mortality in COVID–19 affected old women in comparison to old men. Younger women have the additional advantage of higher levels of the regulator progesterone, along with only one stage escalation of Th1 as compared to older women as well as aged and young men. Part 1 of this research finds that progesterone could favor recovery by interfereing with SARS–CoV–2 infection and COVID–19 pathophysiology at multiple steps. It could be an important remedy itself or as an adjuvant to other antiviral drugs and the symptoms-based treatment protocol. It could be beneficial in COVID–19 patients with pathophysiological indications of immune dysregulation, severe symptoms, and critical illness. It may even have application for vaccination of those with low humoral immunity, to help them raise their antibody titers. The immunity pattern concept may be widely applicable for other diseases, once the specific pattern for a disease is established. Understanding of immunity grading could be of use to evaluate immunity status for other disease conditions. A short summary of the present work would be to consider IPPR (Immunity pattern and progesterone regulation) for COVID–19 patients and to check for presence of the other enlisted parameters affecting cell-mediated immunity and/or progesterone as an alarm for the possibility of severe or critical illness. Further studies based on the clinical applications of the present research in medical practice would be insightful.

Declaration of Competing Interest

None.

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Author's Contributions

Conceptualization of the present research; reference work; published data collection; writing of the manuscript; validation of the concept; visualization and drawing of figures to explain the concepts; reviewing and editing the manuscript; and submission of the work to this journal. No medical writer or editor was involved in the creation of this manuscript.

Human And Animal Rights

No humans or animalsubjects are used for this study.

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References

Abdullah, M., Chai, P.S., Chong, M.Y., 2012. Gender effect on in vitro lymphocyte subset levels of healthy individuals. Cell Immunol 272 (2), 214–219.

Ademe, M., 2020. Immunomodulation for the Treatment of Fungal Infections: Opportunities and Challenges. Front Cell Infect Microbiol 10, 469. doi:10.3389/fcimb.2020.00469, Sep 15.

Akdis, M., Trautmann, A., Klunker, S., Daigle, I., Kucuksezer, U.C., Deglmann, W., Disch, R., Blaser, K., Akdis, C.A., 2003. T helper (Th) 2 predominance in atopic diseases is due to preferential apoptosis of circulating memory/effector Th1 cells. FASEB J 17 (9), 1026–1035.

Allotey, J., Stallings, E., Bonet, M., 2020. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review andmeta-analysis. BMJ 370. doi:10.1136/bmj.m332026, m3320.

Amodio, E., Vitale, F., Cimino, L., Casuccio, A., Tramuto, F., 2020. Outbreak of novel coronavirus (SARS-Cov-2): first evidences from international scientific literature and pending questions. Healthcare (Basel Switz) 8, 517.

Ardia, D.R., Parmentier, H.K., Vogel, L.A., 2011. The role of constraints and limitation in driving individual variation in immune response. Functional Ecology 25, 61–73.

Aurwein–Teissl, M., Lung, T.L., Marx, F., 2002. Lack of antibody production following immunization in old age: Association with CD8CD28 T cell clonal expansions and an imbalance in the production of Th1 and Th2 Cytokines. J Immunol 168, 5893–5899 23.

Bahl, A., Johnson, S., Chen, N.W., 2021. Timing of corticosteroids impacts mortality in hospitalized COVID-19 patients. Intern Emerg Med (5) 1–11.

Barbagallo, M., Shan, J., Pang, P.K.T., Resnick, L.M., 1995. DHEAS effects on VSMC cytosolic free calcium and vascular contractility. Hypertension 26, 1065–1069.

Bekic, S., Martinek, V., Talapko, J., Majnaric, L., Vasolj, M.M.S., 2020. kerleci. Atopic dermatitis and comorbidity. Healthcare (Basel) 8 (2), 70 doi.1-.3390/jealthcare8020070.

Belkaid, Y., Hand, T.W., 2014. Role of the microbiota in immunity and inflammation. Cell 157 (1), 121–141.

Belsky, J.A., Tullius, B.P., Lamb, M.G., Sayegh, R., Stanek, J.R., Auletta, J.J., 2021. COVID-19 in immunocompromised patients: A systematic review of cancer, hematopoietic cell and solid organ transplant patients. J Infect 82 (3), 329–338.

Berger, A., 2000. Th1 and Th2 responses: what are they? BMJ 321 (7258), 424. doi:10.1136/bmj.321.7258.424.

Burtis, C.A., Ashwood, R.E., 1999. Tietz textbook of clinical chemistry. Philadelphia. WB Saunders Co.

Cagnacci, A., Xholli, A., 2020. Age–related difference in the rate of coronavirus disease 2019 mortality in women versus men. Am J ObstetGynecol 223 (3), 453–454.

Canonico, M., Oger, E., Plu–Bureau, G., 2007. Hormone therapy and venous thromboembolism among postmenopausal women: Impact of the route of estrogen administration and progestogens: The ESTHER study. Circulation 115 (7), 840–845.

CDC COVID-19 response team, 2020. Severe outcomes among patients with coronavirus disease 2019 (COVID-19) - United States. Morb Mortal Wkly Rep 69 (12), 343–346.

Cecchini, R., Cecchini, A.L., 2020. SARS–CoV–2 infection pathogenesis is related to oxidative stress as a response to aggression. Med Hypotheses 143, 110102. doi:10.1016/j.mehy.2020.110102.

Chan, Y.H., Fong, S.W., Poh, C.M., Carissimo, G., Yeo, N.K., Amrun, S.N., 2021. Asymptomatic COVID-19: disease tolerance with efficient anti-viral immunity against SARS-CoV-2. EMBO Mol Med 13 (6). doi:10.15252/emmm.202114045, e14045.

Cheng M.H., Zhang S., Porritt R.A., Arditi M., Bahar I., An insertion unique to SARS-CoV-2 exhibits superantigenic character strengthened by recent mutations. Preprint. bioRxiv. 2020 doi:10.1101/2020.05.21.10927220.

Cook, I.F., 2008. Sexual dimorphism of humoral immunity with human vaccines. Vaccine 26, 3551–3555 29-30.

Corona, G., Pizzocaro, A., Vena, W., 2021. Diabetes is most important cause for mortality in COVID-19 hospitalized patients: Systematic review and meta-analysis. Rev EndocrMetabDisord 22 (2), 275–296.

Costa, F.F., Rosário, W.R., Ribeiro Farias, A.C., de Souza, R.G., Duarte Gondim, R.S., Barroso, W.A., 2020. Metabolic syndrome and COVID-19: An update on the associated comorbidities and proposed therapies. Diabetes MetabSyndr 14 (5), 809–814.

Crimeen-Irwin, B., Scalzo, K., Gloster, S., Mottram, P.L., Plebanski, M., 2005. Failure of immune homeostasis – the consequences of under and over reactivity. Curr Drug Targets Immune EndocrMetabolDisord 5 (4), 413–422.

Cron, R.Q., 2020. Coronavirus is the trigger, but the immune response is deadly. Lancet Rheumato 2 (7) E370 -1.
Cuchacovich, M., Tchernitchin, A., Gatica, H., Wurgaft, R., Valenzuela, C., Cornejo, E., 1988. Intraarticular progesterone: effects of a local treatment for rheumatoid arthritis. J Rheumatol 15 (4), 561–565.
Delmonte, O.M., Castagnoli, R., Calzoni, E., Notarangelo, L.D., 2019. Inborn Errors of Immunity With Immune Dysregulation: From Bench to Bedside. Front Pediatr 7, 353. doi:10.3389/fped.2019.00353.
Desai, M.K., Brinton, R.D., 2019. Autoimmune disease in women: Endocrine transition and risk across the lifespan. Front Endocrinol (Lausanne) 10, 265. doi:10.3389/fendo.2019.00265, Published 2019 Apr 29.
Ding, T., Zhang, J., Wang, T., 2020. Potential influence of menstrual status and sex hormones on female SARS-CoV-2 infection: A cross-sectional study from multicenter in Wuhan, China. Clin Infect Dis doi:10.1093/cid/ciaa1022.
D'Silva, K.M., Serling–Boyd, N., Wallwork, R., 2020. Clinical characteristics and outcomes of patients with coronavirus disease 2019 (COVID-19) and rheumatic disease: a comparative cohort study from a US 'hot spot'. Ann Rheum Dis 79, 1156–1162.
Entrenas Castillo, M., Entrenas Costa, L.M., Vaquero Barrios, J.M., 2020. "Effect of calcifediol treatment and best available therapy versus best available therapy on intensive care unit admission and mortality among patients hospitalized for COVID-19: A pilot randomized clinical study". J Steroid Biochem Mol Biol 203, 105751. doi:10.1016/j.jsbmb.2020.105751.
Faas, M., Bouman, A., Moesa, H., Heineman, M.J., de Leij, L., Schuiling, G., 2000. The immune response during the luteal phase of the ovarian cycle: A Th2-type response? FertilSteril 74 (5), 1008–1013.
Farmakis, D., Giakoumis, A., Polymeropoulos, E., Aessopos, A., 2003. Pathogenetic aspects of immune deficiency associated with beta-thalassemia. Med Sci Monit 9 (1) RA19-22.
Faulkner, L., Cooper, A., Fantino, C., Altmann, D.M., Sriskandan, S., 2005. The mechanism of superantigen-mediated toxic shock: Not a simple Th1 cytokine Storm. J Immunol 175 (10), 6870–6877.
Favalli, E.G., Ingegnoli, F., Lucia, O.D., Cincinelli, G., Cimaz, R., Caporali, R., 2020. COVID-19 infection and rheumatoid arthritis: Faraway, so close!. Autoimmu Rev 19 (5), 102523. doi:10.1016/j.autrev.2020.102523.
Ferrando–Martínez, S., Ruiz–Mateos, E., Hernández, A., 2011. Age–related deregulation of naive T cell homeostasis in elderly humans. Age (Dordr) 33 (2), 197–207.
Fishman, M.A., Perelson, A.S., 1999. Th1/Th2 differentiation and cross-regulation. Bulletin Math Biol 61 (3), 403–436.
Galanello, R., Origa, R., 2010. Beta-thalassemia. Orphanet J Rare Dis 5, 11. doi:10.1186/1750-1172-5-11.
Genazzani, A.R., Petraglia, F., Bernardi, F., 1998. Circulating levels of allopregnanolone in humans: gender, age, and endocrine influences. J Clin Endocrinol Metab 83 (6), 2099–2103.
Ghasemnejad–Berenji, H., Ghaffari, N.M., 2018. Immunomodulatory effects of hydroxychloroquine on Th1/Th2 balance in women with repeated implantation failure. Biomed Pharmacother 107, 277–285.
Global Health 50/50 the sex, gender and covid-19 project. Men, sex, gender and COVID-19, 2020. doi:globalhealth.org/the-sex-gender-and-covid-19-project/men-sex-gender-and-covid-19/.
Gomez, C.R., Nomellini, V., Kovacs, E.J., 2019. Sex Hormones and Immunosenescence. In: Fulop, T., Franceschi, C., Hirokawa, K., Pawelec, G. (Eds.), Handbook of Immunosenescence. Springer, Cham.
Grasselli, G., Zangrillo, A., Zanella, A., 2020. The COVID-19 Lombardy ICU Network. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy Region. Italy. JAMA 323 (16), 1574–1581.
Guihot, A., Litvinova, E., Autran, B., Debré, P., Vieillard, V., 2020. Cell–mediated immune responses to COVID–19 infection. Front Immunol 11, 1662. doi:10.3389/fimmu.2020.01662.
Gursoy, A.Y., Caglar, G.S., Kiseli, M., Pabuccu, E., Candar, T., Demirtas, S., 2015. CRP at early follicular phase of menstrual cycle can cause misinterpretation for cardiovascular risk assessment. Intern Med Appl Sci 7 (4), 143–146.
Haberman, R.H., Castillo, R., Chen, A., 2020. COVID-19 in patients with inflammatory arthritis: A prospective study on the effects of comorbidities and disease-modifying antirheumatic drugs on clinical outcomes. Arthritis Rheumatol doi:10.1002/art.41456, Jul 28.
Hall, O., Klein, S., 2017. Progesterone-based compounds affect immune responses and susceptibility to infections at diverse mucosal sites. Mucosal Immunol 10, 1097–1107.
Hameed, I., Masoodi, S.R., Mir, S.A., Nabi, M., Ghazanfar, K., Ganai, B.A., 2015. Type 2 diabetes mellitus: From a metabolic disorder to an inflammatory condition. World J Diabetes 6 (4), 598–612.
Hayashi, K., Miyamoto, A., Konari, A., Ohtani, M., Fukui, Y., 2003. Effect of local interaction of reactive oxygen species with prostaglandin F2α on the release of progesterone in ovine corpora lutea in vivo. Theriogenology 59, 1335–1344.
Hichri, O., Laurin, J.C., Julien, C.A., Joseph, V., Bairam, A., 2012. Dose dependent effect of progesterone on hypoxic ventilatory response in newborn rats. In: Nurse, C, Gonzalez, C, Peers, C, Prabhakar, N. (Eds.), Arterial Chemoreception. Advances in Experimental Medicine and Biology. Springer, Dordrecht 758.
Holcar, M., Goropevšek, A., Ihan, A., Avčin, T., 2015. Age–related differences in percentages of regulatory and effector T lymphocytes and their subsets in healthy individuals and characteristic STAT1/STAT5 signaling response in helper T lymphocytes. J Immunol Res doi:10.1155/2015/352934.
Holtorf, K., 2009. The bioidentical hormone debate: are bioidentical hormones (estradiol, estriol, and progesterone) safer or more efficacious than commonly used synthetic versions in hormonereplacement therapy? Postgrad Med 121 (1), 73–85.
Horstman, A.M., Dillon, E.L., Urban, R.J., Sheffield–Moore, M., 2012. The role of androgens and estrogens on healthy aging and longevity. J Gerontol Biol Sci Med Sci 67 (11), 1140–1152.
Hu, J., Zhang, Z., Shen, W.J., Azhar, S., 2010. Cellular cholesterol delivery, intracellular processing and utilization for biosynthesis of steroid hormones. NutrMetab (Lond) 7, 47 Jun 1doi: 10.1186/1743-7075-7-47. PMID: 20515451; PMCID: PMC2890697.
Jain, A., Chaurasia, R., Sengar, N.S., 2020. Analysis of vitamin D level among asymptomatic and critically ill COVID-19 patients and its correlation with inflammatory markers. Sci Rep 10, 20191. doi:10.1038/s41598-020-77093-z.
Jiang, X., Rayner, S., Luo, M., 2020. Does SARS-CoV-2 has a longer incubation period than SARS and MERS? J Med Virol 92, 476–478.
Jin, J.M., Bai, P., He, W., 2020. Gender Differences in Patients With COVID-19: Focus on severity and mortality. Front Public Health 8, 152. doi:10.3389/fpubh.2020.00152.
Joshua D., Milner, Chapter 15 - Primary immune deficiencies associated with a Th2 diathesis, Editor(s): Kathleen E. Sullivan, E. Richard Stiehm, Stiehm's Immune Deficiencies (Second Edition) Academic Press, 2020: 393-410, ISBN 9780128167687, doi:10.1016/B978-0-12-816768-7.00015-6.
Kaslow, D.C., 2020. Certainty of success: three critical parameters in coronavirus vaccine development. npj Vaccines 5, 42. doi:10.1038/s41541-020-0193-6.
Keswani, A., Dhana, K., Rosenthal, J.A., Moore, D., Mahdavinia, M., 2020. Atopy is predictive of a decreased need for hospitalization for coronavirus disease 2019. Ann Allergy Asthma Immunol 125 (4), 479–481.
Kim, C., Jadhav, R.R., Gustafson, C.E., 2019. Defects in antiviral T cell responses inflicted by aging-associated miR-181a deficiency. Cell Rep 29 (8), 2202–2216.
Kim, C.H., 2015. A functional relay from progesterone to vitamin D in the immune system. DNA Cell Biol 34 (6), 379–382.
Kimura, H., Francisco, D., Conway, M., 2020. Type 2 inflammation modulates ACE2 and TMPRSS2 in airway epithelial cells. J Allergy Clin Immunol 146 (1), 80–88.
Kini, U., Nandeesh, B.N., 2012. Physiology of Bone Formation, Remodeling, and Metabolism. In: Fogelman, I., Gnanasegaran, G., van der Wall, H. (Eds.), Radionuclide and Hybrid Bone Imaging. Springer, Berlin, Heidelberg doi:10.1007/978-3-642-02400-9-225.
Kinoshita, H., Durkee-Shock, J., Jensen-Wacgsoress, M., Kankate, V.V., Lang, H., Lazarski, C.A., 2021. Robust antibody and T cell responses to SRAS-CoV-2 in patients with antibody deficiency. J clin Immunol doi:10.1007/s10875-021-1046-y.
kishoreN Rizvi, V., kishore, N., Sharma, B.B., 1978. Effects of oral contraceptives alpha-1 antitrypsin activity. J ObstetrGynaec India 28 (2), 258–260.
Koff W.C., Williams M.A., Covid-19 and immunity in aging populations — A new research agenda. NEJM 2020 doi:10.1056/NEJMp2006761.
Kosmaczewska, A., Swierkot, J., Ciszak, L., 2014. Patients with the most advanced rheumatoid arthritis remain with Th1 systemic defects after TNF inhibitors treatment despite clinical improvement. Rheumatol Int 34 (2), 243–253.
Kuru M., Kükürt A., Oral H., Öğün M. Clinical use of progesterone and its relation to oxidative stress in ruminants. Book: Sex hormones in Neurodegenerative Processes and Diseases. Editor GorazdDrevenšek, Publisher: IntechOpen 2018 doi:10.5772/intechopen.73311.
Kweon, S.M., Sohn, D.H., Park, J.H., 2018. Male patients with rheumatoid arthritis have an increased risk of osteoporosis: Frequency and risk factors. Medicine (Baltimore) 97 (24). doi:10.1097/MD.0000000000011122, e11122.
Latman, N.S., 1983. Relation of menstrual cycle phase to symptoms of arthritis. American J Medicine 74, 957–960.
Leon–Icaza, S.A., Zeng, M., Rosas–Taraco, A.G., 2019. microRNAs in viral acute respiratory infections: immune regulation, biomarkers, therapy, and vaccines. ExRNA 1, 1. doi:10.1186/s41544-018-0004-7.
Li, H., Llera, A., Malchiodi, E.L., Mariuzza, R.A., 1999. The structural basis of T cell activation by superantigens. Annu Rev Immunol 17, 435–466.
Liu, J., Cao, R., Xu, M., 2020. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. Cell Discov 6 (16). doi:10.1038/s41421-020-0156-0.
Liu, K., Chen, Y., Lin, R., Han, K., 2020. Clinical features of COVID-19 in elderly patients: A comparison with young and middle-aged patients. J Infect 80 (6) e14-e18.
Liu, Y., Mao, B., Liang, S., 2020. Association between age and clinical characteristics and outcomes of COVID-19. Eur Respir J 55 (5). doi:10.1183/13993003.01112-2020, 2001112.
McCusker, C., Upton, J., Warrington, R., 2018. Primary immunodeficiency. Allergy Asthma Clin Immunol 14 (2), 61. doi:10.1186/s13223-018-0290-5.
Memoalia J Anjum, B., Singh, N., Gupta, M., 2018. Decline in pulmonary function tests after menopause. J menopausal med 24 (1), 34–40.
Metra, M., Teerlink, J.R., Voors, A.A., 2009. Vasodilators in the treatment of acute heart failure: what we know, what we don't. Heart Fail Rev 14 (4), 299–307.
Michaud, M., Balardy, L., Moulis, G., 2013. Proinflammatory cytokines, aging, and age-related diseases. J Am Med Dir Assoc 14 (12), 877–882.
Mollard, E., Pedro, S., Chakravarty, E., Clowse, M., Schumacher, R., Michaud, K., 2018. The impact of menopause on functional status in women with rheumatoid arthritis. Rheumatology 57 (5), 798–802.
Monreal, E., Sainz de la Maza, S., Natera-Villalba, E., Beltrán-Corbellini, Á., Rodríguez-Jorge, F., Fernández-Velasco, J.I., 2021. COVID-HRC group. High versus standard doses of corticosteroids in severe COVID-19: a retrospective cohort study. Eur J Clin Microbiol Infect Dis 40 (4), 761–769.
Muneyyirci–Delale, O., Dalloul, M., Nacharaju, V.L., Altura, B.M., Altura, B.T., 1999. Serum ionized magnesium and calcium and sex hormones in healthy young men: importance of serum progesterone level. Fertility Steriltity 72, 817–822.
Nishimura, R., Sakumoton, R., Tatsukawa, Y., Acosta, T.J., Okuda, K., 2006. Oxygen concentration is an important factor for modulating progesterone synthesis in bovine corpus luteum. Endocrinology 147, 4273–4280.
Núñez–de la, M.A., Chatterton, R.T., Choudhury, O.A., Napolitano, D.A., Bentley, G.R., 2007. Childhood conditions influence adult progesterone levels. PLoS Med 4 (5). doi:10.1371/journal.pmed.0040167, e167.

Ottoson, U.B., Carlstrom, K., Damber, J.E., von Schoultz, B., 1984. Serum levels of progesterone and some of its metabolites including deoxycorticosterone after oral and parenteral administration. Br J ObstetGynaecol 91 (11), 1111–1119.
Ouyang, Y., Yin, J., Wang, W., 2020. Down-regulated gene expression spectrum and immune responses changed during the disease progression in COVID-19 patients. Clin Infect Dis 70. doi:10.1093/cid/ciaa462, ciaa462.
Pangrazzi, L., Weinberger, B., 2020. T cells, aging and senescence. Experimental Gerontology 134, 110887. doi:10.1016/j.exger.2020.110887.
Pecins–Thompson, M., Keller–Wood, M., 1997. Effects of progesterone on blood pressure, plasmavolume, and responses to hypotension. Am J Physiol 272, R377–R385 1 Pt 2.
Peng Y., Wan L., Fan C., Cholesterol metabolism–impacts on SARS CoV-2 infection prognosis. 2021 Medrxiv. doi:10.1101/2020.04.16.20068528.
Qin, C., Zhou, L., Hu, Z., 2020. Dysregulation of immune response in patients with COVID-19 in Wuhan, China. Clin Infect Dis 12. doi:10.1093/cid/ciaa248, ciaa248.
Raharusun, P., Priambada, S., Budiarti, C., Agung, E., Budi, C., 2020. Patterns of COVID-19 mortality and vitamin D: An Indonesian study. SSRN Electronic J doi:10.2139/ssrn.3585561.
Ramirez, V.D., Dluzen, D., 1987. Is progesterone a pre-hormone in the CNS? J Steroid Biochem 27 (1-3), 589–598.
Sakata–Kaneko, S., Wakatsuki, Y., Matsunaga, Y., Usui, T., Kita, T., 2000. Altered Th1/Th2 commitment in human CD4+ T cells with ageing. Clin Exp Immunol 120 (2), 267–273.
Scala, E., Abeni, D., Tedeschi, A., 2020. Atopic status protects from severe complications of COVID-19. Allergy doi:10.1111/all.14551.
Schock, H., Zeleniuch–Jacquotte, A., Lundin, E., 2016. Hormone concentrations throughout uncomplicated pregnancies: a longitudinal study. BMC Pregnancy Childbirth 16 (1), 146. doi:10.1186/s12884-016-0937-5.
Schulze–Koops, H., Kalden, J.R., 2001. The balance of Th1/Th2 cytokines in rheumatoid arthritis. Best Pract Res Clin Rheumato 15 (5), 677–691.
Shah, S., Bossois, M., Roby, R., 2015. Swine flu (H1N1 infection): An autoimmune endocrine condition in pregnant females. International J Health & Allied Sciences 4 (1), 9–12.
Sharma, G., Goodwin, J., 2006. Effect of aging on respiratory system physiology and immunology. Clin Interv Aging 1 (3), 253–260.
Shi, Y., Wang, Y., Shao, C., 2020. COVID–19 infection: the perspectives on immune responses. Cell Death Differ 27, 1451–1454 19.
Shields, A.M., Burns, S.O., Savic, S., Richter, A.G., 2021. OK PIN COVID-19 consortium. COVID-19in patients with primary and secondary immunodeficiency: The United Kingdom experience. J allergy clinical immunology 147 (3), 870–875 e1.
Spelsberg, T.C., Subramaniam, M., Riggs, B.L., Khosla, S., 1999. The actions and interactions of sex steroids and growth factors/cytokines on the skeleton. Mol Endocrinol 13 (6), 819–828.
Su, C., Yang, T., Wu, Z., Zhong, J., Huang, Y., Huang, T., Zheng, E., 2017. Differentiation of T-helper cells in distinct phases of atopic dermatitis involves Th1/Th2 and Th17/Treg. European Journal of Inflammation 15 (1), 46–52.
Sun, D.W., Zhang, D., Tian, R.H., 2020. The underlying changes and predicting role of peripheral blood inflammatory cells in severe COVID-19 patients: a sentinel? Clin Chim Acta 508, 122–129.
Surendar, J., Mohan, V., Rao, M.M., Babu, S., Aravindhan, V., 2011. Increased levels of both Th1 and Th2 cytokines in subjects with metabolic syndrome (CURES-103). Diabetes TechnolTher 13 (4), 477–482.
Szekeres–Bartho, J., Barakonyi, A., Par, G., Polgar, B., Palkovics, T., Szereday, L., 2001. Progesterone as an immunomodulatory molecule. Int Immunopharmacol 1 (6), 1037–1048.
Tajima, K., Miura, K., Ishiwata, T., 2011. Sex hormones alter Th1 responses and enhance granuloma formation in the lung. Respiration 81 (6), 491–498.
Thangamani, S., Kim, M., Son, Y., 2015. Cutting edge: progesterone directly upregulates vitamin D receptor gene expression for efficient regulation of T cells by calcitriol. J Immunol 194 (3), 883–886.
Toumba, M., Sergis, A., Kanaris, C., Skordis, N., 2007. Endocrine complications in patients with Thalassaemia Major. Pediatr Endocrinol Rev 5 (2), 642–648.
Tufan, A., Avanoğlu, G.A., Matucci–Cerinic, M., 2020. COVID-19, immune system response,hyperinflammation and repurposing antirheumatic drugs. Turk J Med Sci 50, 620–632 SI-1.
Unfer, V., diRenzo, G.C., Gerli, S., Casini, M.L., 2006. The use of progesterone in clinical practice: evaluation of its efficacy in diverse indications using different routes of administration. Current Drug Therapy 1, 211–219.
Valentino, R., Savastano, S., Tommaselli, A.P., 1993. Hormonal pattern in women affected by rheumatoid arthritis. J Endocrinol Invest 16, 619–624.
vanRoon, J.A.G., Bijlsma, J.W.J., 2002. Th2 mediated regulation in RA and the spondyloarthropathies. Annals Rheumatic Diseases 61, 951–954.
Veisi, A., Bagheri, A., Eshaghi, M., Rikhtehgar, M.H., Rezaei Kanavi, M., Farjad, R., 2021. Rhino-orbital mucormycosis during steroid therapy in COVID-19 patients: A case report. Eur J Ophthalmol doi:10.1177/11206721211009450, Apr.
Virlogeux, V., Fang, V.J., Wu, J.T., 2015. Brief report: Incubation period duration and severity of clinical disease following severe acute respiratory syndrome coronavirus infection. Epidemiology 26 (5), 666–669.
Vitale, G., Salvioli, S., Franceschi, C., 2013. Oxidative stress and the ageing endocrine system. Nat Rev Endocrinol 9 (4), 228–240.
Wardhana, S.E.E., Datau, E.A., Ongkowijaya, J., Karema–Kaparang, A.M., 2013. Transdermal bioidentical progesterone cream as hormonal treatment for osteoarthritis. Acta Med Indones 45 (3), 224–232.
Watkins, R.R., Lemonovich, T.L., Salata, R.A., 2015. An update on the association of vitamin D deficiency with common infectious diseases. Can J PhysiolPharmacol 93 (5), 363–368.
Wewers, M.D., Gadek, J.E., Keogh, B.A., Fells, G.A., Crystal, R.G., 1986. Evaluation of danazol therapy for patients with PiZZ alpha-1-antitrypsin deficiency. Am Rev Respir Dis 134 (3), 476–480.
Wheaton, W.W., Chandel, N.S., 2011. Hypoxia. 2. Hypoxia regulates cellular metabolism. Am J Physiol Cell Physiol 300 (3), C385–C393.
Wood, P., Groom, G., Moore, A., Ratcliffe, W., Celby, C., 1985. Progesterone assays: guidelines for the provision of a clinical biochemistry service. Ann Clin Biochem 22, 1–24.
Wu, H.J., Wu, E., 2012. The role of gut microbiota in immune homeostasis and autoimmunity. Gut Microbes 3 (1), 4–14.
Xue, M., Xie, J., Liu, L., 2019. Early and dynamic alterations of Th2/Th1 in previously immunocompetent patients with community-acquired severe sepsis: a prospective observationalstudy. J Transl Med 17, 57. doi:10.1186/s12967-019-1811-9.
Yang, D., Han, Z., Oppenheim, J.J., 2017. Alarmins and immunity. Immunol Rev 280 (1), 41–56.
Yomogida, K., Chou, Y.K., Chu, C.Q., 2013. Superantigens induce IL-17 production from polarized Th1 clones. Cytokine 63 (1), 6–9.
Zeng, F., Dai, C., Cai, P., 2020. A comparison study of SARS-CoV-2 IgG antibody between male and female COVID-19 patients: A possible reason underlying different outcome between sex. J Med Virol 92, 2050–2054.
Zhou, R., Li, F., Chen, F., 2020. Viral dynamics in asymptomatic patients with COVID-19. Int J Infect Dis 96, 288–290.
Zumoff, B., Miller, L., Levin, J., 1990. Follicular-phase serum progesterone levels of nonsmoking women do not differ from the levels of nonsmokingmen. Steroids 55 (12) 557-9. 22.