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The effect of IGF-1 plasma concentration on COVID-19 severity

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ABSTRACT

Background: The severity and fatality of Coronavirus disease 2019 (COVID-19) infection are not the same in the infected population. The host immune response and Immune-stimulating factors appear to play a role in COVID-19 infection outcome. insulin-like growth factor-1 (IGF-1) affects the immune system by controlling the endocrine system. Recently, the effect of IGF-1 levels on COVID-19 prognosis has been considered.

Objective: To investigate the difference between circulating IGF-1 and inflammatory cytokines concentration among COVID-19 patients, infected patients admitted to the Intensive Care Unit (ICU) (n = 40; 35 ± 5 y) and patients with mild cases of COVID-19 (n = 40; 35 ± 5 y) were screened prior to participation in the study. There was no significant difference between the groups in terms of gender and preexisting inflammatory state. Collected samples were evaluated by ELISA for IGF-1 and IL-6.

Results: The study outcomes included a significant decrease in IGF-1 and an increase in IL-6 serum concentration, as an inflammatory marker, for infected patients admitted to the Intensive Care Unit (ICU) (P ≤ 0.001). Finally, there was a significant increase in the IGF-1 and a decrease in the IL-6 serum concentration of hospitalized patients.

Discussion: it appears that inflammatory cytokines (IL-6) serum concentration in the severe form of coronavirus-based infections causes reduced defenses because of suppressed IGF-1.

Conclusions: Our findings show that lower IGF-1 concentrations are associated with a Severe form of COVID-19 disease. It seems, IGF-1 supplementation or anti-inflammatory treatment rescued the severe form of COVID-19 infection. Further studies are required to determine how to design COVID-19 therapeutic strategies targeting the IGF-1 pathway.

1. Introduction

In late 2019, an unknown infection has spread with lightning speed across the globe, with massive consequences. The sequencing of infected people’s samples revealed that the patients were infected with the novel coronavirus (COVID-19) [1]. COVID-19 affects people in different ways. Most sufferers have self-limiting infections and recover without hospitalization. In contrast, some have severe symptoms and even lost their lives. The deteriorating condition of some sufferers is mainly attributed to unbridled inflammatory damage caused by cytokine storm, uncontrolled immune response, leading to acute respiratory distress syndrome (ARDS). On the other hand, systemic inflammation of COVID-19 has a potentially fatal side effect in patients [2,3]. It seems any factor that regulates the immune system responses can modulate the consequences of COVID-19 infection [4]. It is a well-known fact that the neuroendocrine system has a central role in regulating immune responses [5,6]. endocrine mechanisms of action such as insulin-like growth factor I (IGF-I), prolactin (PRL), and growth hormone (GH) play a critical role in immune network regulation. On the other hand, these factors are known as modulators of immune function. These

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factors are synthesized and secreted by different immune cells. In addition, immune cells express a specific receptor for IGF-I, GH, and PRL. As a result, these factors can modulate the humoral and cellular immune responses by stimulation and proliferation of immunocompetent cells [7]. Previous studies have confirmed the activity of IGF-1 in lung tissue. In other words, IGF-1 signaling plays an essential role in lung development. Studies have shown that IGF-1 is implicated in various diseases, including metabolic disorders, congenital disorders, inflammation, fibrosis, cancers, acute lung injury (ALI), and ARDS [8–10]. While the role of GH and IGF-1 is currently unknown in COVID-19, it has been known to modulate influenza A mediated lung injury in rats [11]. Recombinant IGF-1 infusion in the mice significantly downregulated IL-6 and TNF-α expression [12]. Elevated concentrations of inflammatory cytokines such as IL-6, TNF-α have been introduced as one of the major causes of ARDS in COVID-19 infected patients. Therefore, effectively suppressing the cytokine storm is important to prevent disease deterioration and reduce COVID-19 mortality [13]. Though reduced IGF-1 has not been demonstrated, it has been speculated as a possible risk factor for people with COVID-19 [14]. Herein, we hypothesize that IGF-1 remodels and can regulate severe COVID-19 infection.

2. Materials and methods

Verbal and written informed consent was obtained from participants before starting the study, approved by the ethics board of the Aja University of Medical Sciences. The data that support the findings of this study are available from the corresponding author.

2.1. Participants

To investigate the difference between circulating IGF-1 and IL-6 concentration among COVID-19 patients, 40 infected patients admitted to the Intensive Care Unit (ICU) and 40 patients with asymptomatic and mild cases of COVID-19 were identified before participation in the study. According to the guideline, the nasopharyngeal swab for COVID-19 RT-PCR was obtained from all patients. Eligibility criteria included being 30–40 y, no drug or alcohol addictions. There was no significant difference between the groups in terms of gender. Besides, patients with known a preexisting inflammatory state such as malignancy and concurrent infection were excluded. Critically ill patients with COVID-19 were admitted to the ICU of Hajar hospital in Tehran, Iran. A total of 40 patients with asymptomatic and mild cases of COVID-19 who were also living in Tehran were recruited using the cluster sampling method.

2.2. Blood sampling and immuno-serological analyses

Blood samples (5 mL) were obtained from patients after an overnight fast by a certified phlebotomist. Blood samples were centrifuged at 1500 rpm, for 15-min, at 4 °C, and the resultant serum was collected in 1.5-mL plastic tubes (Eppendorf®) and stored in an Ultra-Low Temperature Freezer (ULT) (−80 °C). Immuno-serological assessments of inflammatory markers of IL-6 and IGF-1 are quantified by human enzyme-linked immunosorbent assay (ELISA) kits specified by the manufacturer (R&D System; Minneapolis, MN, USA) per standard protocol outlined by a blinded technician. The standard curve was created for each ELISA experiment by making serial dilutions of the standard sample whose concentration is accurately known. Each plotted standard curve was used to determine the concentration of the measured analyte from the optical density (OD) measurements.

2.3. Statistical analysis

Statistical analyses were performed using SPSS® version 24 (IBM North America, New York, NY, USA). Throughout the manuscript, data are presented as mean (SD) or mean change (95% CI). The normality test was used to confirm the normality and homogeneity of variances. A comparison of IGF-1 levels between study groups was made with the unpaired student’s t-test. The same test was done to compare IL-6 levels in two groups. The Pearson correlation analysis was performed to examine the association between changes in IGF-1 with IL-6. P values less than 0.05 were considered significant.

3. Results

3.1. Different levels of IL-6 in COVID-19 patients

IL-6 assessment results showed that there was a significant increase in IL-6 levels in infected patients admitted to the ICU group compared to patients with mild cases of COVID-19 (P < 0.05). Serum levels of IL-6 were measured in order to determine the level of inflammation in SARS-CoV-2 infection (Fig. 1).

3.2. IGF-1

Plasma IGF-1 concentration was significantly different between infected patients admitted to the ICU and patients with mild cases of COVID-19. A significant decrease was observed in serum levels of IGF-1 in COVID-19 infected group (P < 0.0001) (Fig. 2). There was a significant negative association between the serum levels of IGF-1 and IL-6 in COVID-19 infected patients admitted to the ICU (r = −0.7367, P < 0.001). The same significant inverse relationship was observed in mild COVID-19 patients (r = −0.4557, P < 0.003) (see Fig. 3).

4. Discussion

Several lines of evidence demonstrate that endocrine mechanisms of action such as IGF-1, PRL, and GH remodel inflammatory diseases and can induce inflammatory cytokines secretion [7]. Herein, we measured levels of IGF-1 as one of the possible regulators of the immune system. Our main findings show that IGF-1 is suspected to modulate inflammation and is associated with the severe form of COVID-19 infection. In fact, in patients with mild cases of COVID-19, there were improved inflammatory factors associated with the higher concentrations of IGF-1.
The present finding corroborates a previous study by Fan et al., which reported that higher IGF-1 concentrations are associated with a lower risk of COVID-19 infection mortality [15]. Other studies have supported the view that IL-6 in infectious diseases causes reduced defenses because of suppressed IGF-1 [14]. Ye et al. reported that cytokine storm in COVID-19 infected people mediated by IL-6 also suppresses IGF-1 [16]. Studies on laboratory model animals have shown that knocked out IGF-1 gene significantly reduces the size of laboratory models [17]. In previous studies, it was found that ARDS is associated with IGF-1 levels in critically ill patients [18], additionally, Serum IGF-1 levels in the ARDS group increased significantly compared with healthy controls [10]. IGF-1 and IGFBP-3 were decreased in at-risk patients and those with late ARDS [19]. Soliman et al. reported that IGF-1 was lower in survivors after COVID19 infection in the elderly transplanted recipients [20]. It was shown in a previous study that, Level of IGF-1 was negatively associated with the mortality risk of ARDS cases [21], blocking antibody of IGF-1R causes dose-dependent apoptosis of primary human lung fibroblasts [22]. Among ARDS patients, IGF-1 levels were significantly lower in patients with severe forms of the disease than in recovered individuals [21]. administration of recombinant human IGF-1 increases capillary permeability of the retina and the skin in the normal population [23]. Mesenchymal stem cell secretory factors ameliorate lipopolysaccharide -linked lung damage through paracrine mechanisms, including IGF-1. The healing process is performed by reducing lung inflammation and enhancing the M2 macrophage phenotype to suppress inflammation and wound repair [24]. While increasing IGF-1 mRNA expression in lung tissues and raised levels of IGF-1 in bronchio-alveolar fluid have been found in Patients with ARDS [25]. Also, it has been shown that IGF-1 increase in lung injury and mortality in Spanish flu (H1N1 influenza infection) [11].

Levels of IGF-1 decrease with age [26]. it seems a high level of circulating IGF-1 is one of the reasons that children get COVID-19 with mild symptoms. In addition, based on the present study results, increasing IGF-1 can play an essential role in modulating the symptoms of the COVID-19. Supplements such as Zinc [27], vitamin D [28], and also Berberis vulgaris juice [29] can elicit increases in IGF-1 in humans. They may help improve the COVID-19 symptoms. Additionally, a monoclonal antibody directed against the IGF-1R, Teprotumumab, may reduce lung injury and death related to COVID-19 [25]. Taken together, these findings suggest that IGF-1 can play an essential role in the consequences of COVID-19 infections outcome by remodeling inflammatory factors secretion profiles. Furthermore, these insights suggest novel therapeutic strategies, IGF-1 increasing/mimicking factors, for predicting disabilities associated with COVID-19 infection and, possibly, cytokine syndromes.

Clinical implications

Our findings show that increased IGF-1 levels can moderate the severe form of the COVID-19. The present results suggest that a novel therapeutic strategy that IGF-1 pathway activation or mimic specific cytokines may effectively treat any failure associated with cytokine storm such as COVID-19. More studies are required to determine whether and how targeting the IGF-1 pathway might improve COVID-19 prognosis.

Ethics approval

The study protocol and consent documents were approved by the ethics board of the Aja University of Medical Sciences.
Disclosure summary

The authors have nothing to disclose.

CRediT authorship contribution statement

Ebrahim Hazrati: Conceptualization. Mohammad Gholami: Investigation, Resources. Ramin Hamidi Farahani: Funding acquisition. Khodayar Ghorban: Writing – original draft. Morteza Ghoyamzadeh: Writing – review & editing. Negin Hosseini Rouzbahani: Supervision, 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.

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