Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Microbial Pathogenesis 164 (2022) 105416

Contents lists available at ScienceDirect

Microbial Pathogenesis

journal homepage: www.elsevier.com/locate/micpath

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

Ebrahim Hazrati [a], Mohammad Gholami [b,c], Ramin Hamidi Farahani [d], Khodayar Ghorban [e,c], Morteza Ghayomzadeh [f], Negin Hosseini Rouzbahani [e,c,*]

[a] Department of Anesthesiology and Critical Care, Faculty of Medicine, Aja University of Medical Sciences, Tehran, Iran
[b] Department of Medical Microbiology, Faculty of Medicine, Aja University of Medical Sciences, Tehran, Iran
[c] Infectious Diseases Research Center, Aja University of Medical Sciences, Tehran, Iran
[d] Department of Infectious and Tropical Diseases, Faculty of Medicine, Aja University of Medical Sciences, Tehran, Iran
[e] Department of Medical Immunology, Faculty of Medicine, Aja University of Medical Sciences, Tehran, Iran
[f] Murdoch Applied Sports Science Laboratory, Murdoch University, Perth, Western Australia, Australia

ARTICLE INFO

Keywords:
IGF-1
COVID-19
SARS-CoV-2
Coronavirus infection
Immune system response

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) ($P \leq 0.001$). 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 corona virus-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

* Corresponding author. Department of Medical Immunology, Faculty of Medicine, Aja University of Medical Sciences, Tehran, Iran.
E-mail addresses: Mohammadg19@gmail.com (M. Gholami), morteza_ghayomzadeh@yahoo.com (M. Ghayomzadeh), n-hosseini@razi.tums.ac.ir (N.H. Rouzbahani).

https://doi.org/10.1016/j.micpath.2022.105416
Received 20 June 2021; Received in revised form 18 January 2022; Accepted 19 January 2022
Available online 26 January 2022

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 being30-40 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 immumo-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©, Hamburg, Germany) 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 in 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.

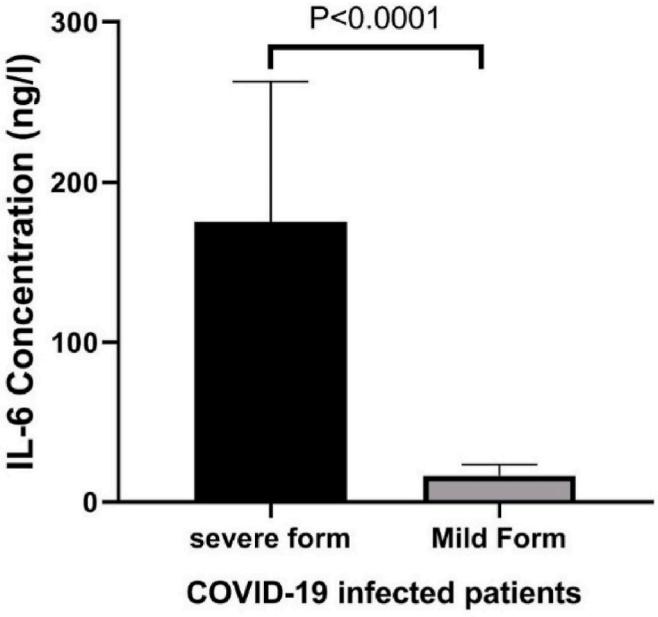

Fig. 1. Comparison of Serum levels of IL-6 in patients with severe and mild COVID-19. The statistical analysis was done using the unpaired student's t-test. P: Shows significant differences with P < 0.0001. IL6: interleukin 6; COVID-19: Coronavirus Disease 2019.

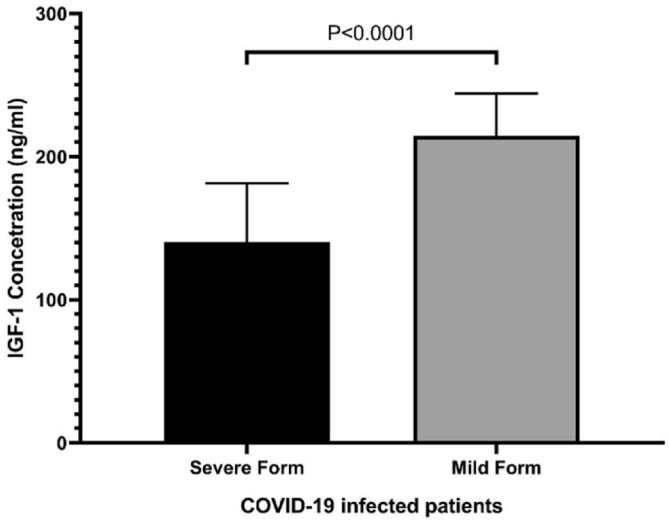

Fig. 2. Comparison of Serum levels of IGF-1 in patients with severe and mild COVID-19. The statistical analysis was done using the unpaired student's t-test. P: Shows significant differences with $P < 0.05$. IGF-1: insulin-like growth factor-1; COVID-19: Coronavirus Disease 2019.

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-1increase 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.

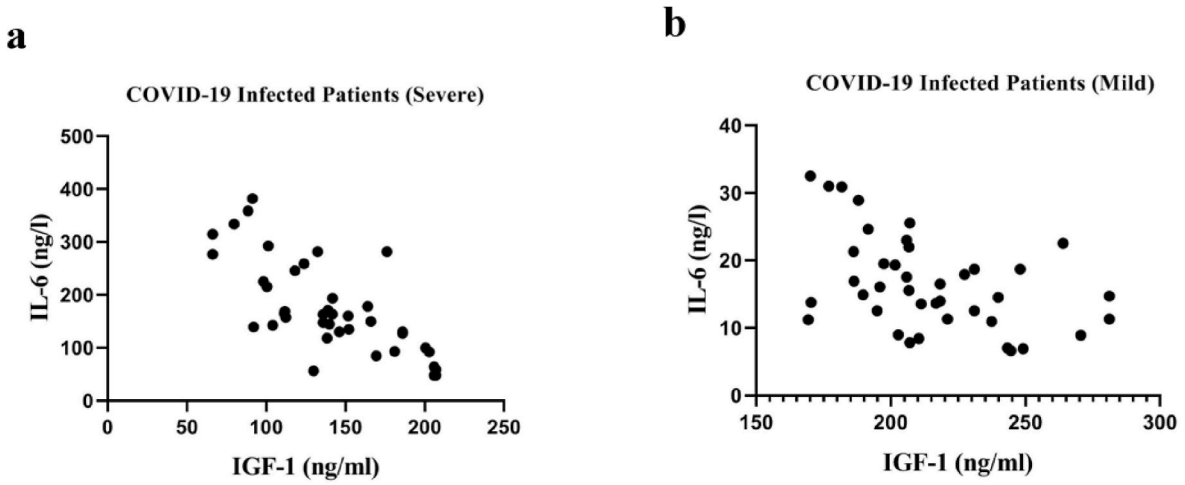

Fig. 3. Correlation of IGF-1 and IL-6 in COVID-19 patients. a, there was a significant negative association between the serum levels of IGF-1 and IL-6 in patients with severe COVID-19 ($r = -0.7367$, $P < 0.001$). **b,** significant inverse relationship was also observed in mild COVID-19 patients ($r = -0.4557$, $P < 0.003$). The statistical association, between two continuous variables (IGF-1 and, IL-6) was performed with Pearson correlation analysis. P: Shows significant differences with $P < 0.05$. IGF-1: insulin-like growth factor-1; IL-6: interleukin 6; COVID-19: Coronavirus Disease 2019.

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 Ghayomzadeh:** 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.

Acknowledgments

We thank our colleagues at Aja University of Medical Sciences for their kind assistance. No financial support was received for the present study.

References

[1] C. Huang, Y. Wang, X. Li, L. Ren, J. Zhao, Y. Hu, et al., Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China, Lancet 395 (10223) (2020) 497–506.
[2] A.K. Azkur, M. Akdis, D. Azkur, M. Sokolowska, W. van de Veen, M.-C. Brüggen, et al., Immune response to SARS-CoV-2 and mechanisms of immunopathological changes in COVID-19, Allergy 75 (7) (2020) 1564–1581.
[3] R. Hamidi Farahani, M. Gholami, E. Hazrati, N. Hosseini Rouzbahani, Z. Hejripour, S. Soleiman-Meigooni, et al., Clinical features of ICU admitted and intubated novel corona virus-infected patients in Iran, Archiv. Clin. Infect. Dis. 15 (2) (2020).
[4] F. Yazdanpanah, M.R. Hamblin, N. Rezaei, The immune system and COVID-19: Friend or foe? Life Sci. (2020), 117900.
[5] H.P.P. Srinivasan ThyagaRajan, Bidirectional communication between the neuroendocrine system and the immune system: relevance to health and diseases, Ann. Neurosci. 19 (1) (2012) 40.
[6] J.I. Webster, L. Tonelli, E.M. Sternberg, Neuroendocrine regulation of immunity, Annu. Rev. Immunol. 20 (1) (2002) 125–163.
[7] C.J. Auernhammer, C.J. Strasburger, Effects of growth hormone and insulin-like growth factor I on the immune system, Eur. J. Endocrinol. 133 (6) (1995) 635–645.
[8] J. Allen, C. Bloor, R. Kedia, R. Knight, M. Spiteri, Expression of growth hormone-releasing factor, growth hormone, insulin-like growth factor-1 and its binding proteins in human lung, Neuropeptides 34 (2) (2000) 98–107.
[9] A.D. Stiles, A.J. D'Ercole, The insulin-like growth factors and the lung, Am. J. Respir. Cell Mol. Biol. 3 (2) (1990) 93–100.
[10] P.M. Krein, P.J. Sabatini, W. Tinmouth, F.H. Green, B.W. Winston, Localization of insulin-like growth factor-I in lung tissues of patients with fibroproliferative acute respiratory distress syndrome, Am. J. Respir. Crit. Care Med. 167 (1) (2003) 83–90.
[11] G. Li, L. Zhou, C. Zhang, Y. Shi, D. Dong, M. Bai, et al., Insulin-like growth factor 1 regulates acute inflammatory lung injury mediated by influenza virus infection, Front. Microbiol. 10 (2019) 2541.
[12] S. Sukhanov, Y. Higashi, S.-Y. Shai, C. Vaughn, J. Mohler, Y. Li, et al., IGF-1 reduces inflammatory responses, suppresses oxidative stress, and decreases atherosclerosis progression in ApoE-deficient mice, Arterioscler. Thromb. Vasc. Biol. 27 (12) (2007) 2684–2690.
[13] D. Ragab, H. Salah Eldin, M. Taeimah, R. Khattab, R. Salem, The COVID-19 cytokine storm; what we know so far, Front. Immunol. 11 (2020) 1446.
[14] G. Steinman, COVID-19 and autism, Med. Hypotheses 142 (2020) 109797.
[15] X. Fan, C. Yin, J. Wang, M. Yang, H. Ma, G. Jin, et al., Pre-diagnostic circulating concentrations of insulin-like growth factor-1 and risk of COVID-19 mortality: results from UK Biobank, medRxiv (2020).
[16] Q. Ye, B. Wang, J. Mao, The pathogenesis and treatment of theCytokine Storm'in COVID-19, J. Infect. 80 (6) (2020) 607–613.
[17] D. Accili, J. Nakae, J.J. Kim, B.C. Park, K.I. Rother, Targeted gene mutations define the roles of insulin and IGF-I receptors in mouse embryonic development, J. Pediatr. Endocrinol. Metab. 12 (4) (1999) 475–485.
[18] A.M. Ahasic, P. Tejera, Y. Wei, L. Su, C.S. Mantzoros, E.K. Bajwa, et al., Predictors of circulating insulin-like growth factor-1 and insulin-like growth factor binding protein-3 in critical illness, Crit. Care Med. 43 (12) (2015) 2651.
[19] G. Andonegui, P.M. Krein, C. Mowat, R. Brisebois, C. Doig, F.H. Green, et al., Enhanced production of IGF-I in the lungs of fibroproliferative ARDS patients, Physiol. Rep. 2 (11) (2014), e12197.
[20] A.R. Soliman, K.M. Sadek, Relation between insulin growth factor 1 and survival after SARS-CoV-2(COVID 19) infection in elderly kidney transplant recipients, Ren. Fail. 43 (1) (2021) 388–390.
[21] A.M. Ahasic, R. Zhai, L. Su, Y. Zhao, K.N. Aronis, B.T. Thompson, et al., IGF1 and IGFBP3 in the acute respiratory distress syndrome, European J Endocrinol European Federat. Endocrine Soc. 166 (1) (2012) 121.
[22] L.M. Schnapp, S. Donohoe, J. Chen, D.A. Sunde, P.M. Kelly, J. Ruzinski, et al., Mining the acute respiratory distress syndrome proteome: identification of the insulin-like growth factor (IGF)/IGF-binding protein-3 pathway in acute lung injury, Am. J. Pathol. 169 (1) (2006) 86–95.
[23] M.A. Hussain, K. Studer, E.P. Messmer, E.R. Froesch, Treatment with insulin-like growth factor I alters capillary permeability in skin and retina, Diabetes 44 (10) (1995) 1209–1212.
[24] L. Ionescu, R.N. Byrne, T. van Haaften, A. Vadivel, R.S. Alphonse, G.J. Rey-Parra, et al., Stem cell conditioned medium improves acute lung injury in mice: in vivo evidence for stem cell paracrine action, Am. J. Physiol. Lung Cell Mol. Physiol. 303 (11) (2012) L967–L977.
[25] B.J. Winn, Is there a role for insulin-like growth factor inhibition in the treatment of COVID-19-related adult respiratory distress syndrome? Med. Hypotheses 144 (2020), 110167.
[26] N.M. Ashpole, J.E. Sanders, E.L. Hodges, H. Yan, W.E. Sonntag, Growth hormone, insulin-like growth factor-1 and the aging brain, Exp. Gerontol. 68 (2015) 76–81.
[27] J. Guo, J. Xie, B. Zhou, M.-A. Găman, H. Kord-Varkaneh, C.C.T. Clark, et al., The influence of zinc supplementation on IGF-1 levels in humans: a systematic review and meta-analysis, J. King Saud Univ. Sci. 32 (3) (2020) 1824–1830.
[28] C. Trummer, V. Schwetz, M. Pandis, M.R. Grübler, N. Verheyen, M. Gaksch, et al., Effects of vitamin D supplementation on IGF-1 and calcitriol: a randomized-controlled trial, Nutrients 9 (6) (2017) 623.
[29] S. Pirouzpanah, S. Asemani, A. Shayanfar, B. Baradaran, V. Montazeri, The effects of Berberis vulgaris consumption on plasma levels of IGF-1, IGFBPs, PPAR-γ and the expression of angiogenic genes in women with benign breast disease: a randomized controlled clinical trial, BMC Compl. Alternative Med. 19 (1) (2019) 324.