IL-6 Level and the Risk of Arthritis after COVID Infection

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DOI: 10.47750/pnr.2022.13.S06.320

Abstract

We aimed to assess the prognosis on the onset of arthritis in the diabetic patient after severe SARS-CoV-2 infection.

Methods: The medical data of 10 patients with type 2 diabetes melitus, obese or overweight, hospitalized, in the interval between 1st of February and 31st of July 2021 at ``Saint Spyridon`` County Hospital Iasi, Romania for SARS-Cov-2 infection with were analyzed.

Results: Although all the patients received treatment with tocilizumab 8 mg/kg body during 30 days, the blood analysis showed very high level of interleukins 6, and the joint painful symptoms continued to be manifested. The interleukins 6 serum level is higher and persistent in diabetic patient with SARS-CoV-2 infection, against the background of pre-existing chronic inflammation induced by diabetes, obesity and the glycemic imbalance. This renders the cytokine release syndrome difficult to control in the diabetic patients with severe infections, which leads to a higher hazard of interleukin 6 transcription errors. SARS-CoV-2 diabetic patients run the risk of developing long-term arthritis due to the uncontrolled, permanent synthesis of this cytokine.

Conclusion: The immunologic modifications associated with the severe coronavirus infection acting on the predisposing genetic background (HLA-DR4/DR1), might underlie the onset of the arthritis on the long-term due to the exaggerated activation of IL-6 and the chronicity of the inflammation it generates. Studies shall be required that monitor on the long-term the diabetic patients surviving a severe Sars-CoV-2 infection as to the occurrence of the arthritis.

Keywords: SARS-CoV; MERS; SARS-CoV-2; IL-6, arthritis.

INTRODUCTION

Coronaviruses are a group of zoonotic viruses common among animals, which might spread among humans as well. A new strand of this coronavirus, namely SARS-CoV-2, called coronavirus disease 2019 (COVID-19) by the World Health Organization, was discovered in early January of this year in Wuhan [1].

During this pandemic, the SARS-CoV-2 contagiousness rate has exceeded that of both the SARS and MERS viruses (though not mortality, with a rate of 5.58%), and the rate at which the infection is spreading is showing no signs of slowing down [2].

Several studies have elucidated the epidemic features of the infection, and others are underway, aimed at identifying the specific biological traits of this virus. A longer incubation time associated with the SARS-CoV-2 infection was reported and a shorter serial period in comparison with SARS-CoV and MERS-CoV, which led to screening and control-policy adjustments [3].

The spike protein (protein S) of 2019-nCoV2 binds to angiotensin-converting enzyme 2 (ACE2), having the same receptor as SARS-CoV, in order to invade the host cell, while MERS-CoV uses Dipeptidyl-peptidase 4 (DPP4) as a primary receptor, which SARS-CoV-2 has no affinity for. The affinity between ACE2 and SARS-CoV-2 is much stronger than that between SARS-CoV and ACE2, which might explain the fast development and strong human-to-human transmission capacity of COVID-19 [4,5].

According to the Center for Disease Control and Prevention, following an incubation period that might last for 2 to 14 days after exposure, symptoms present as a dry cough, fever, joint and muscle pain, altered general status and even dyspnoea when interstitial pneumonia sets in [6,7].

The SARS-CoV-2 infection pathogeny mechanisms are insufficiently known, but the similarity with the SARS-CoV and MERS-CoV infections helps us better understand and identify the disease's mechanisms. Viral infections are known to induce patterns of reactive arthritis [8]. In addition, patients with moderate to severe COVID-19 have elevated plasma IL-6 levels [9,10], which may induce rheumatic manifestations at a distance from SARS-CoV-2 infection.

The rheumatic symptoms described during COVID are rare and hidden by other manifestations of the infection. Most often, they are arthralgias in the early stages of the disease [11].

In a study of more than 300 patients with COVID-19, arthralgia and myalgia were found in more than a quarter of cases [12]. Several cases of acute arthritis or dactylitis have been reported, some of which may suggest arthritis, but we can expect an increase in the number of cases in the coming months [13].

The literature presents cases of aseptic arthritis, after severe infection with SARS-CoV 2 that appeared about 3 weeks or a month after the severe infection, with a predominance of men, generally monoarticular, located in the lower limbs or dactylitis. The joint fluid is sterile, without microcrystals. The reported evolution was favourable with NSAID treatment and intra-articular corticosteroid injections. The potential mechanisms of arthritis in the context of SARS-CoV-2 viral infection remain in the hypothetical stage. The presence of the virus could not be detected by RT-PCR in synovial fluid [14–19].

CYTOKINE RELEASE SYNDROME (CRS) AND DIABETES

Diabetes mellitus (DM) is one of the leading causes of morbidity and mortality worldwide. The condition is associated with several macro- and microvascular complications, but it is not known whether DM itself actually increases susceptibility and influences the outcome of infections or cardiovascular and renal comorbidities that are frequently associated with DM are the main factors involved [20]. In the current SARS-CoV-2 pandemic, some studies have not found a clear association between DM and severe disease [21,22]. However, other reports from China [23,24] and Italy [25] have shown that patients older people with chronic diseases, including DM, have a higher risk of severe SARS-CoV-2.

Hyperglycaemia and insulin resistance promote increased synthesis of glycosylation end products (AGEs) and pro-inflammatory cytokines, and oxidative stress stimulates the production of adhesion molecules that mediate tissue inflammation [20,26]. This inflammatory process may be the underlying mechanism that leads to a higher tendency to infections, with worse outcomes in patients with DM [20]. Guo et al. published the first report on the biochemical characteristics of patients with DM and the additional risk that this disease may pose in the progression of SARS-CoV-2 [27].

Interleukin-6 (IL-6) is found among the various cytokines found at significantly higher levels compared to those with normal blood glucose values. This cytokine is already elevated in conditions of chronic inflammation in the diabetic patient and may play a determinant role towards severe evolution of SARS-CoV-2 infection [28]. IL-6 is a pleiotropic cytokine that is primarily involved in acute inflammatory responses, but is also significantly elevated in conditions with chronic inflammation such as metabolic disorders and cardiovascular disease.

The harmful effects of overexpressed IL-6 signalling in a diabetic patient infected with SARS-CoV-2 require the administration of tocilizumab, a monoclonal antibody against the IL-6 receptor approved for the treatment of autoimmune diseases such as giant cell arteritis or severe rheumatoid arthritis, also successfully tested for other autoimmune disorders, such as Graves' disease [23]. Produced primarily at sites of acute and chronic inflammation, IL-6 is released into the serum and induces a transcriptional inflammatory response through the alpha IL-6 receptor. IL-6 is involved in a wide variety of inflammatory conditions associated with inflammation, including DM and arthritis.

Osteoarthritis is a whole-organ disease involving cytokine production by cartilage, synovial membrane, and bone. Cytokines such as tumor necrosis factor alpha (TNF), interleukin 1 beta (IL 1β) and IL 6 are produced by chondrocytes, macrophages, T cells and osteophytes in response to tissue damage. Pro- matrix metalloproteinases, released by synoviocytes and macrophages, are cleaved into matrix metalloproteinases, and further contribute to tissue damage. IL 1β, TNF and IL 6 enter the bloodstream; osteoarthritis is therefore a systemic disease. T cells and B cells are recruited by the cytokine milieu in the synovial fluid and contribute to local synovitis. Bone cells release several cytokines, most notably IL 6 and receptor activator of nuclear factor κB ligand (RANKL) [29].

CASES PRESENTATION

This study was performed during 6 months (between 1st of February and 31st of July 2021) in ``Saint Spyridon`` County Hospital Iasi, Romania on the hospitalized patients with SARS-CoV-2 infection and type 2 DM. The data of 10 patients, aged between 42 and 77 years, diagnosed with type 2 DM and medium and severe forms of SARS-CoV-2 infection, treated with tocilizumab 8 mg/kg body weight were collected and evaluated. The investigation consisted of the patients medical data computerized evidence retrospective analysis. The investigation was conducted in agreement with the Declaration of Helsinki and approved by the Committee for Research and Ethical Issues of the 'Grigore T. Popa' University of Medicine and Pharmacy Iasi for studies involving patients (Certificate No. 30/14.01.2021). The researches carried out followed the approval by the ethics commission of Saint Spyridon County Hospital Iasi, Romania and the condition for informed consent was surrendered based on the type of the investigation, comprising in retrospectively evaluation of the electronic data of the patients' medical sheets, which were hospitalized during 6 months. The information was examined anonymously, the protocol of the investigation states that there was no direct contact of investigators to patients. Accordingly, we obtained the approval of the hospital for performing the study and disseminating the results gained without the requirement for an informed consent [30].

The clinical manifestations were represented by respiratory symptoms, but also included joint pain with various localizations.

A number of 6 patients had moderate forms of SARS-CoV-2 infection, and 4 had severe forms. Oxygen (O2) saturations (SpO2%) ranged from 90–97%. Three patients were noted with class 3 obesity, two with class 1 obesity, and 5 were overweight (Table 1).

Table 1. Clinical evaluation of patients with type 2 DM and SARS-CoV-2 infection

Pacient	Age (Years)	Form of Infection	Hospitalization Period (days)	Weight (Kg)	Height (cm)	Body Mass Index (kg/m^2)	Nutritional Status
1	68	Medium	14	210	177	67	Class 3 obesity
2	71	Medium	18	80	170	27.7	Overweight
3	46	Severe	30	130	173	43.4	Class 3 obesity
4	77	Severe	21	87	172	29.4	Overweight
5	50	Medium	14	80	170	27.7	Overweight
6	62	Severe	22	80	160	31.3	Class 1 obesity
7	48	Medium	14	90	165	33.1	Class 1 obesity
8	65	Severe	24	75	160	29.3	Overweight
9	56	Medium	14	85	170	29.4	Overweight
10	42	Medium	18	110	165	40.4	Class 3 obesity

Blood glucose values were above the normal limit with variations between 125 mg/dL and 555 mg/dL. Serum IL-6 was maintained at levels ranging from 35.4 to 347.9 pg/mL (normally 6 pg/mL), and hospitalization days between 14 and 30 days.

Inflammation parameters had values above the normal limit: reactive protein c between 16.7 and 142.88 (normal < 0.5 mg/dL), erythrocyte sedimentation rate between 35 and 110 mm/h (normal 10 mm/hour), fibrinogen between 390 and 658 mg/dL (normally 200–400 mg/dL). We analysed D-dimers as a coagulation assessment parameter, the values were between 0.298 and 0.835 μg/mL (normal < 0.5 μg/mL) (Table 2).

Table 2. Paraclinical evaluation of patients with type 2 DM and SARS-CoV-2 infection

Pacient	Glucose (mg/dL)	C-Reactive Protein (mg/dL)	IL-6 (pg/mL)	Erythrocyte Sedimentation Rate (mm/h)	D-Dimers (μg/mL)	Fibrinogen (mg/dL)	O2 Saturation (SpO_2%)	Joint Pain
1	181	23.68	61.25	70	0.605	461	97	Yes
2	555	142.88	75.06	70	0.540	461	93	Yes
3	193	81.84	59.2	110	0.298	658	92	Yes
4	179	78.3	347.9	90	0.803	39	90	Yes
5	129	44.58	43.98	50	0.835	478	97	Yes
6	187	16.7	35.44	35	0.344	411	94	Yes
7	131	79.21	53.8	47	0.578	420	95	Yes
8	125	36.75	240.4	85	0.675	550	93	Yes
9	138	28.4	41.78	75	0.754	445	92	Yes
10	185	37.5	71.25	42	0.621	621	94	Yes

DISCUSSIONS

The infection caused by the new virus from the corona family is still the subject of numerous studies and investigations. Humankind is facing a pandemic affecting an ever-increasing number of people, caused by a new viral agent that affects the immune system via incompletely elucidated mechanisms.

We evaluated 10 cases of SARS-CoV-2 infection in patients diagnosed with type 2 DM, who had moderate to severe forms of the disease [31]. The symptoms also included joint pain with various localizations. All patients presented imbalances of serum glucose values and persistent inflammatory syndrome. DM and obesity induce a chronic inflammation status in the body.

We believe that SARS-CoV-2 infection can trigger autoimmunity phenomena due to chronic inflammation with various manifestations, including arthritis, especially in patients who have joint manifestations during the infection.

The long-term consequences of this infection cannot be anticipated with certainty [32]. We do not know (and therefore cannot state with certainty) whether this SARS-CoV-2 infection will lead to chronicity of certain inflammatory phenomena or activation of autoimmunity. We cannot make indubitable statements related to the persistence of the virus within the body and its potential to reactivate. We also do not know if the persistence of the virus in the body can perpetuate inflammatory phenomena against the background of pre-existing inflammation in the diabetic patient.

We now know that when the virus reaches cells, it blocks infected cells' capacity to respond and activate antiviral mechanisms. It appears that the immune response is delayed due to a viral strategy [33]. The virus manages to escape and delay the immune response, effectively creating a window of opportunity during which the virus multiplies and disseminates within the tissues.

After massive multiplication, the bodily response occurs in the form of intense inflammation, accompanied by a sudden and exaggerated increase in pro-inflammatory cytokines. IL-6, a cytokine produced by various cells of the human body (macrophages, lymphocytes, astrocytes, ischemic myocytes, endothelial cells) has both pro-inflammatory and anti-inflammatory properties, being a key component in regulating various physiologic and pathological processes [34].

CONCLUSIONS

CRS is difficult to control in patients with severe infections, which leads to an increased risk of IL-6 transcription disturbances.

Considering the disturbances caused by SARS-CoV-2 in the operation of the immune system, long-term monitoring of the risk of developing arthritis due to uncontrolled and continuous IL-6 synthesis needs to be carried out.

Analysing the similarity between SARS-CoV and MERS-CoV and SARS-CoV-2, in terms of clinical and laboratory data, one might expect that in the long term, SARS-CoV-2 will trigger diseases with autoimmune etiopathogenesis such as arthritis especially due to its persistence in the body and the risk of reactivation of the infection.

ACKNOWLEDGEMENTS. This work is part of Irina Claudia Anton's PhD studies and was partial financially supported by The Doctoral School of "Grigore T. Popa" University of Medicine and Pharmacy, Iasi, Romania (Doctoral Grant financing approval 1.02.2021).

ETHICAL APPROVAL (WHERE EVER APPLICABLE).

The investigation was conducted in agreement with the Declaration of Helsinki and approved by the Committee for Research and Ethical Issues of the 'Grigore T. Popa' University of Medicine and Pharmacy Iasi for studies involving patients (Certificate no. 30/14.01.2021). The researches carried out followed the approval by the ethics commission of Saint Spiridon County Hospital Iasi, Romania and the condition for informed consent was surrendered based on the type of the investigation, comprising in retrospectively evaluation of the electronic data of the patients' medical sheets, which were hospitalized during 6 months. The information was examined anonymously, the protocol of the investigation states that there was no direct contact of investigators to patients. Accordingly, we obtained the approval of the hospital for performing the study and disseminating the results gained without the requirement for an informed consent.

AUTHORS' CONTRIBUTIONS. Conceptualization and methodology, Ana-Maria Pelin, Liliana Mititelu-Tartau, Irina Claudia Anton; Data analysis and investigation, Irina Claudia Anton, Liliana Mititelu-Tartau, Ramona Oana Rosca, Elena Niculet, Nicoleta-Maricica Maftei, Stefan Rosca; writing—original draft preparation, Ana-Maria Pelin, Liliana Mititelu-Tartau, Ramona Oana Rosca, Elena Niculet, Nicoleta-Maricica Maftei, Stefan Rosca; writing—review and editing, Ana-Maria Pelin, Nicoleta-Maricica Maftei, Liliana Mititelu-Tartau, Alin Tatu; supervision and project administration, Ana-Maria Pelin, Liliana Mititelu-Tartau, Alin Tatu. All authors have read and agreed to the published version of the manuscript.

COMPETING INTERESTS. The authors declare no conflict of interest.

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