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ORIGINAL ARTICLE

The Relationship between post COVID-19 Rheumatological Manifestations and Angiotensin Converting Enzyme 2 Level in Patients with Type 2 Diabetes

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ABSTRACT

BACKGROUND: Coronavirus disease (Covid-19) causes a systemic inflammatory syndrome with pulmonary involvement. Rheumatological involvement in patients with mild clinical forms of Covid-19 is uncertain. Diabetes mellitus (DM) is known to increase susceptibility to viral infections. Also, patients with DM have a reduced Angiotensin converting enzyme 2 (ACE2) expression that might contribute to the increased predisposition to severe lung injury. The aim of the work is to study the rheumatological manifestations with assessment of ACE2 level in post COVID patients with and without diabetes mellitus (DM).

METHODS: We included a total of 160 consecutive patients in Covid-19 convalescent phase (after clinical recovery), all of them diagnosed with a positive PCR test. All participants were divided into two categories: 80 patients with COVID-19 and DM and another 80 patients with COVID-19 without DM. All patients subjected to history taking, clinical assessment, laboratory investigations (including serum ALT, AST, Albumin, Urea, Creatinine, FBG, HBA1c, Procalcitonin, CRP, Hemoglobin, WBC, Platelet count, Neutrophile count, Lymphocyte count, D-Dimer and ACE2).

RESULTS: Patients with DM have a higher significant mean serum level of ACE2 (43.90 ± 20.04). Regarding post COVID rheumatological manifestation, patients with DM have a higher significant severe arthralgia and arthritis with higher significant serum level of anti-nuclear antibody (ANA), rheumatoid factor (RF) and Anti-citrullinated protein (CCP) ($p < 0.05$).

COCLUSIONS: We found that COVID-19 patients with D.M have a higher risk of rheumatological complications with higher level of ACE2 than COVID-19 patients without D.M.

KEYWORDS: Angiotensin; Converting; Enzyme 2; Arthritis; COVID-19; Diabetes; Mellitus.

INTRODUCTION

COVID-19 manifests with a wide range of presentations. Several debilitating manifestations may develop during or after an infection consistent with COVID-19. These manifestations may continue for more than 3 months after COVID-19 infection and usually are not related to an alternative diagnosis **[1].** Common symptoms may include weakness, breathlessness, fatigue, myalgia, joint pain, cognitive blunting, headache, etc. This is called "Long COVID" or more commonly "Post COVID-19 Syndrome (PCS)" **[2].**

Rheumatic symptoms were also reported after other coronavirus infection, such as Middle East respiratory syndrome and severe acute respiratory syndrome (SARS) with an incidence of 32% and 10%, respectively. However, this incidence may be underestimated due to the high doses of glucocorticoids (cumulative doses during hospitalization of more than 1 gm) **[3-4].**

On the other hand, there is a role for angiotensin-converting enzyme 2 (ACE2) in the association between DM and COVID-19. ACE2, a type 1 integral membrane glycoprotein, is constitutively expressed by the epithelial cells of the lungs, kidneys, blood vessels and intestine. In normal physiology, ACE2 breaks down angiotensin-II, and to some extent angiotensin-I, to smaller peptides, angiotensin (1–7) and angiotensin **(1–9),** respectively **[5].** The ACE2/Angiotensin **[1–7]** system has an important antioxidant and anti-inflammatory role protecting the lung against acute respiratory distress syndrome (ARDS). Indeed, ACE2 was protective against lethal avian influenza A H5N1 infection **[6].**

Diabetic patients have a reduced ACE2 expression, possibly due to glycosylation; this might contribute to the increased predisposition to severe lung injury and ARDS with COVID-19 **[7].** Also, patients with connective tissue diseases CTD) are known to have a reduced ACE2 expression, this may be due to the presence of anti-ACE2 antibodies in a significant proportion of CTD patients, genetic polymorphism, epigenetic dysregulation, and the application of drugs especially glucocorticoids **[8]**.

We aimed studying rheumatological manifestations by assessment of ACE2 level in post COVID diabetic and non-diabetic patients.

METHODS

This study was performed at Internal medicine Department, Faculty of Medicine, Menoufia university during the period from May 2021 to May 2022. All participants provided their informed consent. The study has been carried out in accordance with the code of ethics of the world medical association (Declaration of Helsinki) for experiments involving humans. The ethics committee (institutional review board, Faculty of medicine, Menoufia University) gave their approval to the research (approval number: 12/2022 INTM 3-2).

a total of 160 consecutive patients in Covid-19 convalescent phase (after clinical recovery) were included, all of them were positive PCR test, according to recommendations of the World Health Organization. Our patients were divided into two categories: eighty (80) COVID-19 patients were type 2 DM, and the remaining eighty (80) COVID-19 patients were none-diabetic.

All patients subjected to full history taking, clinical assessment and laboratory investigations (including serum alanine transaminase (ALT), aspartate aminotransferase (AST), Albumin, Urea, Creatinine, fasting blood glucose (FBG), hemoglobin A1c (HbA1c), Procalcitonin, C-reactive protein (CRP), and Hemoglobin (Hb), D-Dimer and ACE2 levels, white blood cells (WBCs), Platelet (PLT), Neutrophile, and Lymphocyte count, and Computerized Tomography (CT) on the chest.

Type 2-DM was diagnosed according to American Diabetes Association Guidelines, with FBG more than 126 mg/dl, 2 hours postprandial blood glucose more than 200 mg/dl and/or HBA1c more than 6.5 mg% **[9].**

Only patients diagnosed with COVID-19 and needed ward admission were included. While; who needed admission in the intensive care units (ICU), with history of autoimmune diseases, with renal and/or liver failure were excluded.

Serum protein levels of ACE2 were measured using the slow off rate modified aptamer (SOMAmer) based protein profiling technology, performed at SomaLogic Inc. Blood samples were collected after an overnight fast. We prepared serum using a standardized protocol, stored in 0.5 ml aliquots at 80°C and serum samples that were used for the protein measurements. Hybridization controls were used to correct systematic variability in detection and calibrator samples of three dilution sets (40%, 1%, and 0.005%) were included so that the degree of fluorescence was a quantitative reflection of protein concentration.

Statistical analysis:

Data were analyzed using IBM SPSS software package version 20.0. **(**Armonk, NY: IBM Corp**)**. Kolmogorov-Smirnov test was used to test data for normality. Categorical data were represented as numbers and percentages. Distributed data were expressed as range (minimum and maximum), mean, standard deviation and median. The following tests were used; Student t-test, Mann Whitney test, Chi-square test, and Fisher Exact test.

P value was used to assess the level of significance. P value > 0.05 was considered statistically non-significant. P value< 0.05 was considered statistically significant. P value< 0.001 was considered statistically highly significant.

RESULTS

One hundred and sixty patients with COVID-19 were included, and according to Prescence of absence of diabetes mellites type 2; were divided into two equal each group include 80. There was no significant difference among diabetic and non-diabetic as regard; age and sex, hypertension, whoever; asthma and chronic obstructive pulmonary disease (COPD) (p <0.001) were significantly higher in diabetic group **(Table 1).**

Diabetic patients had higher serum levels of ALT, AST, albumin, creatinine, FBG, HbA1c, CRP, Hb and PLT while have lower serum levels of Urea and WBC (p <0.001) **(Table 2).**

Diabetic patients had higher Neutrophile count (11.20 ± 3.18), D-Dimer (0.68 ± 0.20) and ACE2 levels (43.90 ± 20.04) while have a lower Lymphocyte count (0.77 ± 0.25) (p < 0.001) **(Table 3)**.

Patients in Group-1 had more and severe post COVID-19 symptoms and comorbidities in the form of headache, cough, skin rash, chest pain, shortness of breath, fatigue, and myalgia (p < 0.05). Regarding the post COVID-19 rheumatological manifestations, patients with DM have more arthralgia and arthritis with significant high levels of ANA, rheumatoid factor and Anti CCP (p < 0.05) **(Table 4).**

ACE2 level was significantly negatively correlated with FBG (r=-0.255 & P=0.022) and Hb level (r=-0.297& P=0.007) while; showed a significant positive correlation with HbA1c (r=0.237, P=0.034) **(Table 5).**

ACE2 level in post COVID-19 diabetic patients was significantly associated with positive ANA, RF and Anti CCP (p=0.012, 0.002 and 0.001, respectively) while not with arthralgia and arthritis. However, the non-diabetic group; ACE2 level was not associated with positive ANA, RF, Anti CCP, arthralgia and arthritis **(Table 6).**

Table (1): Demographic data of both groups

	Diabetic (n = 80)	**Non-diabetic (n = 80)**	**Test**	**P**
Age (years):				
Mean ± SD.	44.10 ± 9.88	43.80 ± 7.50	t= 0.216	0.829
Range (min. – max.)	43 (25 – 62)	43 (33 – 63)		
Sex:				
Male	48 (60.0%)	40 (50.0%)	χ^2= 1.616	0.204
Female	32 (40.0%)	40 (50.0%)		
Comorbidity:				
Hypertension	40 (50.0%)	40 (50.0%)	χ^2=0.000	1.000
Asthma	24 (30.0%)	12 (15.0%)	χ^2=5.161*	0.023*
COPD	44 (55.0%)	16 (20.0%)	χ^2=20.91*	<0.001*

SD; Standard deviation t; Student t-test χ^2; Chi square test
P; p value for comparing between the two studied Covid 19 groups
*; Statistically significant at p ≤ 0.05. COPD; chronic obstructive pulmonary disease

Table (2): laboratory data in both groups

Laboratory data	Diabetic (n = 80)	Non-diabetic (n = 80)	Test	P
ALT				
Mean ± SD.	62.80 ± 15.25	28.75 ± 10.44	U= 184.0*	<0.001*
Range (min. – max.)	62 (42 – 98)	29 (9 – 61)		
AST				
Mean ± SD.	70.35 ± 17.44	30.05 ± 7.79	U= 64.0*	<0.001*
Range (min. – max.)	67.5 (40 – 99)	29.5 (18 – 48)		
ALB (g/dl)				
Mean ± SD.	3.73 ± 0.60	2.51 ± 0.12	U= 8.00*	<0.001*
Range (min. – max.)	3.75 (2.7 – 5.0)	2.53 (2.17 – 2.78)		
Urea (mg/dl)				
Mean ± SD.	16.05 ± 4.81	30.05 ± 7.79	U= 328.0*	<0.001*
Range (min. – max.)	15.5 (7 – 25)	29.5 (18 – 48)		
Creatinine (mg/dl)				
Mean ± SD.	0.70 ± 0.17	0.53 ± 0.12	U= 1356.0*	<0.001*
Range (min. – max.)	0.65 (0.50 – 1.10)	0.53 (0.28 – 0.80)		
FBG				
Mean ± SD.	222.6 ± 94.81	113.4 ± 22.29	t= 10.028*	<0.001*
Range (min. – max.)	210.5 (71 – 386)	110.5 (81 – 186)		
HbA1c (%)				
Mean ± SD.	8.03 ± 1.33	5.16 ± 0.53	t= 17.955*	<0.001*
Range (min. – max.)	8 (5.5 – 10)	5.20 (4 – 6)		
PCT 0.1 (ng/ml)				
Mean ± SD.	5.16 ± 2.20	0.81 ± 1.21	U= 272.0*	<0.001*
Median (min. – max.)	5.0 (1.10 – 9.50)	0.20 (0.02 – 5.0)		
CRP (mg/l) 6.0				
Mean ± SD.	67.15 ± 30.63	26.90 ± 21.82	U= 768.0*	<0.001*
Range (min. – max.)	55.5 (29 – 135)	21.5 (5 – 76)		
Hb (gm/dl)				
Mean ± SD.	13.22 ± 4.68	11.39 ± 1.37	t= 3.427*	0.001*
Range (min. – max.)	11.80 (9.0 – 29.70)	11.45 (9.30 – 13.70)		
WBCs count(10^6/ml)				
Mean ± SD.	3.70 ± 1.11	5.81 ± 2.25	U= 1368.0*	<0.001*
Median (min. – max.)	3.45 (2.20 – 5.90)	5.79 (2.20 – 10.80)		
PLT count (10^3/ml)				
Mean ± SD.	348.6 ± 157.0	341.8 ± 157.4	U= 3056.0*	<0.001*
Range (min. – max.)	288.5 (146 – 693)	288.5 (146 – 693)		

SD: Standard deviation t: Student t-test U: Mann Whitney test

P; p-value for comparing between the two studied Covid 19 groups. *; Statistically significant; $p \leq 0.05$

Table (3): Comparison between the two studied Covid 19 groups according to different parameters

	Diabetic (n = 80)	Non-diabetic (n = 80)	Test	P
Neutrophils (2.0-8.0)				
Low (<2)	0 (0.0%)	48 (60.0%)	χ^2= 125.091*	<0.001*
Normal (2.0 - 8.0)	12 (15.0%)	32 (40.0%)		
High (>8)	68 (85.0%)	0 (0.0%)		
Mean ± SD.	11.20 ± 3.18	1.99 ± 0.76	U= 0.000*	<0.001*
Range (min. – max.)	11 (7 – 19)	1.80 (1 – 4)		
LYMP (0.8-4.0)				
Low (<0.8)	44 (55.0%)	4 (5.0%)	χ^2= 47.619*	<0.001*
Normal (0.8-4.0)	36 (45.0%)	76 (95.0%)		
Mean ± SD.	0.77 ± 0.25	1.87 ± 0.72	U= 416.0*	<0.001*
Range (min. – max.)	0.70 (0.30 – 1.30)	1.85 (0.70 – 3.70)		
D-Dimer (0.5-1.0)				
Low (<0.5)	12 (15.0%)	48 (60.0%)	χ^2= 36.267*	<0.001*
Normal (0.5 - 1.0)	64 (80.0%)	32 (40.0%)		
High (>1.0)	4 (5.0%)	0 (0.0%)		
Mean ± SD.	0.68 ± 0.20	0.45 ± 0.17	U= 1224.0*	<0.001*
Range (min. – max.)	0.70 (0.30 – 1.10)	0.41 (0.22 – 0.90)		
ACE 2 level				
Mean ± SD.	43.90 ± 20.04	9.85 ± 4.14	U= 176.0*	<0.001*
Range (min. – max.)	44.5 (10 – 90)	8.5 (3 – 19)		

SD: Standard deviation t: Student t-test U: Mann Whitney test
χ^2: Chi square test MC: Monte Carlo FE: Fisher Exact
p: p value for comparing between the two studied Covid 19 groups
*: Statistically significant at $p \leq 0.05$

Table (4): post COVID symptoms and comorbidities in both groups

		Diabetic (n = 80)	Non-diabetic (n = 80)	Test	P
Headache	no	16 (20.0%)	24 (30.0%)	χ^2= 33.486*	<0.001*
	mild	12 (15.0%)	36 (45.0%)		
	moderate	24 (30.0%)	16 (20.0%)		
	severe	24 (30.0%)	4 (5.0%)		
	very Severe	4 (5.0%)	0 (0.0%)		
Cough	no	8 (10.0%)	16 (20.0%)	χ^2= 20.0*	<0.001*
	mild	12 (15.0%)	28 (35.0%)		
	moderate	24 (30.0%)	16 (20.0%)		
	severe	28 (35.0%)	20 (25.0%)		
	very Severe	8 (10.0%)	0 (0.0%)		
Skin rash	no	32 (40.0%)	48 (60.0%)	χ^2= 7.200*	0.027*
	mild	40 (50.0%)	24 (30.0%)		
	moderate	8 (10.0%)	8 (10.0%)		
Chest pain	no	20 (25.0%)	44 (55.0%)	χ^2= 35.311*	<0.001*
	mild	8 (10.0%)	16 (20.0%)		
	moderate	20 (25.0%)	16 (20.0%)		
	severe	16 (20.0%)	4 (5.0%)		

		Diabetic (n = 80)	Non-diabetic (n = 80)	Test	P
	Very Severe	16 (20.0%)	0 (0.0%)		
S.O.B	no	12 (15.0%)	16 (20.0%)	χ^2= 23.771*	<0.001*
	mild	32 (40.0%)	48 (60.0%)		
	moderate	16 (20.0%)	16 (20.0%)		
	severe	16 (20.0%)	0 (0.0%)		
	very Severe	4 (5.0%)	0 (0.0%)		
Fatigue	no	0 (0.0%)	32 (40.0%)	χ^2= 40.348*	<0.001*
	mild	56 (70.0%)	36 (45.0%)		
	moderate	24 (30.0%)	12 (15.0%)		
Myalgia	no	16 (20.0%)	28 (35.0%)	χ^2= 48.750*	<0.001*
	mild	12 (15.0%)	40 (50.0%)		
	moderate	28 (35.0%)	12 (15.0%)		
	severe	8 (10.0%)	0 (0.0%)		
	very severe	16 (20.0%)	0 (0.0%)		
Arthralgia	no	16 (20.0%)	16 (20.0%)	χ^2= 28.038*	<0.001*
	mild	16 (20.0%)	44 (55.0%)		
	moderate	16 (20.0%)	12 (15.0%)		
	severe	32 (40.0%)	8 (10.0%)		
Arthritis	no	16 (20.0%)	12 (15.0%)	χ^2= 25.194*	<0.001*
	mild	16 (20.0%)	44 (55.0%)		
	moderate	20 (25.0%)	16 (20.0%)		
	severe	28 (35.0%)	8 (10.0%)		
ANA	no	28 (35.0%)	52 (65.0%)	χ^2= 14.400*	<0.001*
	yes	52 (65.0%)	28 (35.0%)		
	mean ± SD.	320.0 ± 320.0	160.0 ± 75.42	U= 520.0*	0.029*
	range (Min. – Max.)	320 (80 – 1280)	160 (80 – 320)		
Rheumatoid Factor	no	24 (30.0%)	40 (50.0%)	χ^2= 9.333*	0.025*
	mild	28 (35.0%)	20 (25.0%)		
	moderate	16 (20.0%)	16 (20.0%)		
	severe	12 (15.0%)	4 (5.0%)		
Anti CCP	no	28 (35.0%)	44 (55.0%)	χ^2= 23.898*	<0.001*
	mild	24 (30.0%)	32 (40.0%)		
	moderate	16 (20.0%)	4 (5.0%)		
	severe	12 (15.0%)	0 (0.0%)		

SD: Standard deviation U: Mann Whitney test χ^2: Chi square test
S.O.B: Shortness of breath ANA: Antinuclear Antibody Anti CCP: Anti-Cyclic Citrullinated Peptide Antibody
*: Statistically significant at $p \leq 0.05$

Table (5): Correlation between ACE2 level and different parameters

	ACE2 level			
	Diabetic (n = 80)		Non-diabetic (n = 80)	
	r_s	p	r_s	P
ALT	-0.060	0.595	0.083	0.463
AST	0.065	0.568	-0.053	0.638
ALB (g/dl)	-0.070	0.535	0.038	0.736

	ACE2 level			
	Diabetic (n = 80)		Non-diabetic (n = 80)	
	r_s	p	r_s	P
Urea (mg/dl)	0.062	0.588	-0.053	0.638
CREAT (mg/dl)	0.155	0.169	0.053	0.641
FBG (mg/dl)	-0.255	0.022*	-0.051	0.631
HBA1c (mg%)	0.237	0.034*	0.082	0.462
PCT (ng/ml)	-0.162	0.150	0.220	0.051
CRP (mg/l)	0.099	0.384	0.146	0.195
Hb (gm/dl)	-0.297	0.007*	0.097	0.392
WBCs	0.082	0.467	-0.145	0.198
PLT	0.187	0.098	0.107	0.346

r_s: Spearman coefficient 6*: Statistically significant at $p \leq 0.05$

Table (6): Relation between ACE2 level and different parameters

		ACE2 level							
		n	Diabetic (n = 80)		U (p)	n	Non-diabetic (n = 80)		U (p)
			Mean ±SD.	range			Mean± SD.	Range	
Arthralgia	no	**16**	40.3 ±22.6	40.5 (10 –70)	456.0 (0.500)	**16**	8.8 ±1.3	8 (8 –11)	480.0 (0.698)
	yes	**64**	44.8 ±19.4	44.5 (15 –90)		**64**	10.1 ±4.5	9.5 (3 –19)	
Arthritis	no	**16**	40.3 ± 22.6	40.5 (10 – 70)	456.0 (0.500)	**12**	11.3 ± 5.7	8 (7 – 19)	368.0 (0.587)
	yes	**64**	44.8 ± 19.4	44.5 (15 – 90)		**68**	9.6 ± 3.8	9 (3 – 17)	
ANA	no	**28**	36.4 ± 17.9	44 (10 – 63)	480.0* (0.012*)	**52**	9.8 ± 4.4	8 (3 – 19)	688.0 (0.685)
	yes	**52**	47.9 ± 20.1	50 (20 – 90)		**28**	10.0 ± 3.6	9 (6 – 15)	
RF	no	**24**	33.7 ±13.0	33.5 (10 –50)	376.0* (0.002*)	**40**	9.9 ± 4.7	9.5 (3 – 19)	784.0 (0.877)
	yes	**56**	48.3 ±21.0	51.5 (15 –90)		**40**	9.8 ± 3.5	8 (5 – 15)	
Anti CCP	no	**28**	34.6 ±18.1	33 (10 –70)	408.0* (0.001*)	**44**	10.4 ± 4.8	10 (3 – 19)	680.0 (0.275)
	yes	**52**	48.9 ±19.4	50 (15 –90)		**36**	9.2 ± 3.1	8 (5 – 15)	

SD: Standard deviation, U: Mann Whitney test 90 *: Statistically significant at $p \leq 0.05$

DISCUSSION

Diabetes mellites (DM), and COVID-19 have a bidirectional relationship. Uncontrolled DM increases the severity of COVID-19 and may increase morbidity and mortality. The pandemic of COVID-19 has also been associated with poor DM control, progression from prediabetes to overt diabetes, increased number of new onset diabetes and corticosteroid induced diabetes **[10,11].**

This study evaluated rheumatological manifestations with assessment of ACE2 level in post COVID-19 in type 2 DM, and non-diabetic. Our results concluded that COVID-19 patients with DM have a higher risk of rheumatological complications with higher level of ACE2 than COVID-19 patients without DM.

Diabetic one had a higher significant mean serum level of, D-Dimer and ACE2, and neutrophil count, while had significant lower Lymphocyte count.

In our study, patients with DM had more post COVID-19 symptoms and comorbidities in the form of headache, cough, skin rash, chest pain, shortness of breath, fatigue, and myalgia ($p < 0.05$). Also, had a significant severe arthralgia and arthritis with higher significant serum level of ANA, rheumatoid factor and Anti CCP ($p < 0.05$).

In the same lines, Ghosn and colleagues studied 1137 patients (288 of them were admitted to the intensive care unit) and found that about 60% of them had at least one symptom of dyspnea, fatigue, joint pain, and muscle pain at 6 months [12]. Garrigues and

colleagues analyzed 120 survivors by telephone surveys after a mean of 111 days of admission either to the ICU (n=24) or the hospital ward unit (n=96) and found that they complained from fatigue (54.2%), dyspnea (39.6%), cough (14.6%), insomnia (14.6%) and ageusia (9.4%) [13]. However, these studies included patients admitted in the ICU, while our study included only patients in the ward.

Also, González Hermosillo and colleagues analyzed 130 survivors through telephone surveys and found that common symptoms were fatigue (46.9%), joint pain (43.8%), dyspnea (42.3%), muscle pain (36.2%), anosmia (6.9%), and ageusia (5.4%) at 6 months [14]. Fortini and colleagues also analyzed 59 survivors after a median of 123 days of discharge from the hospital ward unit and observed that they suffered from fatigue (42.4%), dyspnea (37.3%), ageusia (16.9%), anosmia (15.2%), cough (11.9%), joint pain (8.5%), and myalgia (8.5%) [15].

COVID19 patients reported significantly more rheumatic symptoms in comparison to community-dwelling controls, indicating that patients with COVID-19 did not recover even after 12 months of symptom onset. It is well known that viral infection is one of the common causes of arthralgia. Coronaviruses, like many other viruses, can cause varying degrees of joint disease [16]. One large South Korean retrospective study found that several respiratory viral infections by coronavirus, metapneumovirus and parainfluenza virus were associated with an increased number of incident rheumatoid arthritis [17]. However, these studies were not specific for COVID-19.

Published follow-up studies of COVID-19 found that the percentage of self-reported rheumatic symptoms after COVID-19 ranged from 4.5% to 27.3% [18-24]. This varied proportions may be due to the differences in trial designs, the differences in illness severity of the study populations and even the differences in virus strains.

Several hypotheses have been proposed to explain the mechanism of rheumatic symptoms after COVID-19, but the exact mechanism remains unclear. Uncontrolled or excessive cytokine responses in patients with COVID-19, including tumor necrosis factor and interleukin 17 (IL-17), as main therapeutic targets in psoriatic arthritis and spondylarthritis, have an important role in the progress of COVID-19 [25-26].

We demonstrate that diabetic patients with COVID-19 have a higher significant mean serum level of ACE2 than non-diabetic patients.

The risk of critical admissions and mortality with COVID-19 was increased two to three times in patients with higher ACE2 levels in both patients with DM and in patients with impaired fasting glucose [27,28]. There are many reasons for the increased susceptibility to COVID-19 in obese and diabetic patients. This may be due to the impaired immune response found in these patients [29]. Adipose tissue contains ACE2 receptors nearly the same as pulmonary tissues, [30] and in mice, high fat diet increases the expression of ACE2 in adipose tissue [31]. The higher circulating levels of ACE2 in patients with DM reflects increased number of membrane-bound ACE2 receptor and also activity in solid tissues, that may be associated with high viral load in these high-risk groups, and this may be associated with increased susceptibility to adverse outcomes in COVID-19. Thus, in addition to altered ACE2 levels, Type 2 DM and obesity are associated with chronic inflammation that can increase inflammation in pulmonary tissues, which combined may affect the severity of outcome in COVID-19 [32].

Our results included only survivors of COVID-19 who had been admitted in hospital ward unit not outpatient survivors or those who admitted in intensive care unit. However, using ACE2 level as a marker for COVID-19 severity and the effect of DM on post COVID-19 rheumatological manifestations may be a good point.

CONCLUSIONS

COVID-19 diabetic patient had a higher risk of rheumatological complications with a higher level of ACE2 than COVID-19 in non-diabetic one. We concluded that diabetic patients with COVID-19 need more careful follow up.

REFERRENCES

1. Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. JAMA cardiology. 2020; 5(7): 802-10.
2. Shi S, Qin M, Cai Y, Liu T, Shen B, Yang F, Cao S, et al. Characteristics and clinical significance of myocardial injury in patients

with severe coronavirus disease 2019. EHJ. 2020; 41(22): 2070-9.

3. Memish ZA, Perlman S, Van Kerkhove MD, Zumla A. Middle East respiratory syndrome. Lancet 2020; 395: 1063–77.
4. Schett G, Manger B, Simon D, Caporali R. COVID-19 revisiting inflammatory pathways of arthritis. Nat Rev Rheumatol. 2020; 16:465–70.
5. Tikellis C, Thomas MC. Angiotensin-Converting Enzyme 2 (ACE2) Is a Key Modulator of the Renin Angiotensin System in Health and Disease. IJP. 2012; 2012: 1–8.
6. Zou Z, Yan Y, Shu Y, Gao R, Sun Y, Li X, et al. Angiotensin-converting enzyme 2 protects from lethal avian influenza A H5N1 infections. N C [Internet] 2014 [cited 2020 Mar 21];5. Available from: http://www.nature.com/articles/ncomms4594.
7. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk Factors Associated with Acute Respiratory Distress Syndrome and Death in Patients with Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA IM [Internet]; 2020 [cited 2020 Mar 21]; Available from: https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2763184.
8. Tang X, Geng L, Feng X, Sun L. Decreased serum ACE2 levels in patients with connective tissue diseases. *Rheumatology*. 2021; 60(9): 4401–6.
9. Professional Practice Committee. *Standards of Medical Care in Diabetes—2021*. *Diabetes Care.* 2021; 44 (1): S3. https://doi.org/10.2337/dc21-Sppc
10. Unnikrishnan R, Misra A. Diabetes and COVID19: a bidirectional relationship. ND. 2021;11(1): 21. https://doi.org/10.1038/s41387-021-00163-2.
11. Misra A, Ghosh A, Gupta R. Heterogeneity in presentation of hyper glycaemia during COVID-19 pandemic: a proposed classification. DMS.2021;15(1):403e6. https://doi.org/10.1016/j.dsx.2021.01.018.
12. Ghosn J, Piroth L, Epaulard O, Le Turnier P, Mentré F, Bachelet D, Laouénan C. Persistent COVID-19 symptoms are highly prevalent 6 months after hospitalization: results from a large perspective cohort. CMI. 2021 Jul 1;27(7):1041-e1.
13. Garrigues E, Janvier P, Kherabi Y, Le Bot A, Hamon A, Gouze H, et al. Post-discharge persistent symptoms and health-related quality of life after hospitalization for COVID-19. JI. 2020; 81(6): e4-6.
14. González-Hermosillo JA, Martínez-López JP, Carrillo-Lampón SA, Ruiz-Ojeda D, Herrera-Ramírez S, Amezcua-Guerra LM, Martínez-Alvarado MD. Post-acute COVID-19 symptoms, a potential link with myalgic encephalomyelitis/chronic fatigue syndrome: a 6-month survey in a Mexican cohort. BS. 2021;11(6):760.
15. Fortini A, Torrigiani A, Sbaragli S, Lo Forte A, Crociani A, Cecchini P, et al. COVID-19: persistence of symptoms and lung alterations after 3–6 months from hospital discharge. Infection. 2021; 49(5) :1007-15.
16. Marks M, Marks JJC. Viral arthritis. CM (Lond). 2016; 16:129–34.
17. Joo YB, Lim YH, Kim KJ, Park KS, Park YJ. Respiratory viral infections and the risk of rheumatoid arthritis. ART. 2019; 21:199.
18. Carfi A, Bernabei R, Landi F. Gemelli Against COVID-19 Post-Acute Care Study Group. Persistent symptoms in patients after acute COVID-19. JAMA. 2020; 324:603–5.
19. Carvalho-Schneider C, Laurent E, Lemaignen A, Beaufils E, Bourbao-Tournois C, Laribi S, et al. Follow-up of adults with noncritical COVID-19 two months after symptom onset. CMI. 2021; 27:258–63.
20. Arnold DT, Hamilton FW, Milne A, Morley AJ, Viner J, Attwood M, et al. Patient outcomes after hospitalization with COVID-19 and implications for follow-up: results from a prospective UK cohort. Thorax. 2020; 76:399–401.
21. Moreno-Pérez O, Merino E, Leon-Ramirez JM, Andres M, Ramos JM, Arenas-Jiménez J, et al. Post-acute COVID-19 syndrome. Incidence and risk factors: a Mediterranean cohort study. JI. 2021; 82:378–83.
22. Petersen MS, Kristiansen MF, Hanusson KD, Danielsen ME, Á Steig B, Gaini S, et al. Long COVID in the Faroe Islands—a longitudinal

study among non-hospitalized patients. CID. 2021; 73: e4058–63.

23. Stavem K, Ghanima W, Olsen M, Gilboe H, Einvik GJT. Persistent symptoms 1.5-6 months after COVID-19 in non-hospitalized subjects: a population-based cohort study. Thorax. 2020; 76:405–7.
24. Huang C, Huang L, Wang Y, Li X, Ren L, Gu X, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. Lancet. 2021; 397:220–32.
25. Javelle E, Ribera A, Degasne I, Gaüzère B-A, Marimoutou C, Simon F. Specific management of post-chikungunya rheumatic disorders: a retrospective study of 159 cases in Reunion Island from 2006 to 2012. PNTD. 2015; 9: e0003603.
26. Schett G, Manger B, Simon D, Caporali R. COVID-19 revisiting inflammatory pathways of arthritis. NRR. 2020; 16:465–70.
27. Huang I, Lim MA, Pranata R. Diabetes mellitus is associated with increased mortality and severity of disease in COVID-19 pneumonia - a systematic review, meta-analysis, and meta-regression. DMS. 2020;14(4):395-403.
28. Zheng Z, Peng F, Xu B, et al. Risk factors of critical & mortal COVID- 19 cases: a systematic literature review and meta-analysis. JI. 2020; 81(2): e16-e25.
29. Frasca D, Blomberg BB, Paganelli R. Aging, obesity, and inflammatory age-related diseases. FI. 2017; 8: 1745.
30. Sattar N, McInnes IB, McMurray JJV. Obesity is a risk factor for severe COVID-19 infection: multiple potential mechanisms. Circulation. 2020; 142(1): 4-6.
31. Gupte M, Boustany-Kari CM, Bharadwaj K, Police S, Thatcher S, Gong MC, et al. ACE2 is expressed in mouse adipocytes and regulated by a high-fat diet. Am JPRICP. 2008;295(3): R781-R788. HGS. Inflammation and metabolic disorders.

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