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RESEARCH ARTICLE/KLİNİK ÇALIŞMA

FLORA 2022;27(2):324-334 • doi: 10.5578/flora.20229816

Repurposing Sitagliptin for COVID-19 in Adults: Clinical Benefits and An Approach for the Mechanism

Yetişkinlerde COVID-19 Tedavisi İçin Sitagliptin Kullanılması: Klinik Faydalar ve Mekanizma Yaklaşımı

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Cite this article as: *Çınar G, Coşgun Yazgan S, Elhan AH, Akdemir Kalkan İ, Gülten E, Ünal MA, et al. Repurposing sitagliptin for COVID-19 in adults: Clinical benefits and an approach for the mechanism. FLORA 2022;27(2):324-34.*

ABSTRACT

Introduction: *Dipeptidyl peptidase-4 (DPP4) has been shown to be a functional receptor for MERS-CoV. An interaction between the viral spike protein and DPP4 is thought to facilitate viral entry. We aimed to find out whether sitagliptin, a member of DPP4 inhibitors, would have beneficial effects in COVID-19 patients.*

Materials and Methods: *In this single center retrospective study, we evaluated 58 patients of whom 16 were on sitagliptin treatment. Molecular docking studies were performed to identify possible interactions between ACE2 and sitagliptin.*

Results: *Sitagliptin use shortened the time to clinical recovery about 3.5 and fastened viral clearance more than 5 days. Resolution of all symptoms was achieved on a mean±standard error (SE) of 2.50 ± 0.40 days in sitagliptin (+) group and 5.69 ± 0.61 days in sitagliptin (-) group (Log-rank test, p< 0.001). PCR tests for SARS-CoV-2 resulted negative in mean ± SE of 7.50 ± 0.98 days in sitagliptin (+) and 13.17 ± 1.07 days in sitagliptin (-) group (Log-rank test, p= 0.003). Compared to day 0, CRP, ferritin and D-dimer levels on days three, five, and seven were significantly lower whereas lymphocyte count was higher in sitagliptin (+) group.*

Conclusion: *Our results suggest that sitagliptin seems to have a potential to be considered for the treatment of COVID-19.*

Key Words: *COVID-19; DPP4 inhibitors, ACE2; Sitagliptin; SARS-CoV-2*

Received/Geliş Tarihi: 25/02/2022 - Accepted/Kabul Ediliş Tarihi: 16/05/2022

Available Online Date: 08.07.2022

ÖZ

Yetişkinlerde COVID-19 Tedavisi Için Sitagliptin Kullanılması: Klinik Faydalar ve Mekanizma Yaklaşımı

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Giriş: *Dipeptidil peptidaz-4'ün (DPP4) MERS-CoV için fonksiyonel bir reseptör olduğu gösterilmiştir. Viral spike proteini ve DPP4 arasındaki etkileşimin viral girişi kolaylaştırdığı düşünülmektedir. Biz de bu çalışmada DPP4 inhibitörlerinin bir üyesi olan sitagliptinin COVID-19 hastalarında faydalı etkileri olup olmayacağını öğrenmeyi amaçladık.*

Materyal ve Metod: *Bu tek merkezli retrospektif çalışmada, 16'sı sitagliptin tedavisi almakta olan 58 hastayı değerlendirdik. ACE2 ve sitagliptin arasındaki olası etkileşimleri belirlemek için moleküler yerleştirme (docking) çalışmaları yaptık.*

Bulgular: *Sitagliptin kullanımı klinik iyileşme süresini yaklaşık 3.5 gün kısalttı ve viral klirensi beş günden fazla hızlandırdı. Tüm semptomların düzelmesi, sitagliptin (+) grubunda 2.50 ± 0.40 gün ve sitagliptin (-) grubunda 5.69 ± 0.61 gün ortalama ± standart hata (SE) ile sağlandı (Log-rank testi, p< 0.001). SARS-CoV-2 için PCR testleri, sitagliptin (+) grubunda 7.50 ± 0.98 gün ve sitagliptin (-) grubunda 13.17 ± 1.07 gün ortalama ± SE'de negatif sonuçlandı (Log-rank testi, p= 0.003). Sitagliptin (+) grubunda 0. güne göre üçüncü, beşinci ve yedinci günlerde CRP, ferritin ve D-dimer düzeyleri anlamlı olarak düşük, lenfosit sayısı ise daha yüksekti.*

Sonuç: *Sonuçlarımız, sitagliptinin COVID-19 tedavisi için düşünülme potansiyeline sahip olduğunu gösterdi.*

Anahtar Kelimeler: *COVID-19; DPP4 inhibitörleri; ACE2; Sitagliptin; SARS-CoV-2*

INTRODUCTION

SARS-CoV-2 is a new member of Betacoronavirus genra of Coronavirinae within the Coronaviridae family, the causative agent of coronavirus disease 2019 (COVID-19)[1]. Four main structural proteins (S, M, E, and N) are essential for attachment to and fusion with host cell membrane, for virion assembly, and involved in viral pathogenesis[1]. Studies have identified the extracellular protease domain of angiotensin converting enzyme 2 (ACE2) as the receptor for SARS-CoV-2[2]. ACE2 is an integral membrane metallopeptidase initially identified in heart, kidney, and testis. Subsequent studies have shown a much wider distribution including the upper airways, lungs, gut, and liver with various physiological functions[3]. Analysis of a variety of human tissues identified the small intestines, not the lungs, with the highest level of ACE2 expression[4]. The respiratory system as the main target of the virus and the inflammation of the lungs as the primary symptom of patients with SARS-CoV-2 infection suggest a possible involvement of co-receptor(s) to facilitate infection and perhaps additional strategies for treatment. In fact, it is known that the viruses utilize multiple transmembrane proteins of the host cell in addition to the primary receptor[5]. The membrane-associated human dipeptidyl peptidase-4 (DPP4) is recently suggested to interact with the S1 domain of the viral spike glycoprotein as reported by Vankadari *et al*[6].

DPP4 inhibitors are widely used for type 2 diabetes mellitus (T2DM) treatment and act

selectively to inhibit the catalytic activity of cell-related and circulating DPP4. When used in people with T2DM, DPP4 inhibitors provide inhibition of 50-95% DPP4 activity over a 24-hour period[7].

Interestingly, Ahmed A. Al-Qahtani et al. have shown that MERS-CoV infects macrophage cells by binding to the DPP4 receptor via the S glycoprotein and suppresses TNFα and IL-6 production while increasing IL-10. Therefore, the interaction between the spike protein and DPP4 is thought to not only facilitate viral entry, but also to have immunosuppressive effects mediating the spread of the virus[8]. In addition, increased expression/activity of DPP4 are associated with diabetes, obesity and metabolic syndrome, all of which have been reported to affect the severity of COVID-19[9].

These findings along with our clinical observations in a university hospital during COVID-19 pandemic gave rise to the hypothesis that sitagliptin may have a potential to be considered for the treatment of SARS-CoV-2 infection. Thus, we aimed to find out whether sitagliptin use would be beneficial in COVID-19 patients. Molecular docking studies were performed to explain a possible interaction between ACE2 and sitagliptin, as well.

MATERIALS and METHODS

Study Design and Setting

Seventy-two consecutive adult patients (>18 y) admitted to a university hospital in XXX, XXX, from 1 April to 1 May 2020 with respiratory symptoms and confirmed of COVID-19 by a positive PCR test were enrolled in this retrospective cohort study. Oral informed consents were obtained from all patients included in the study. The study protocol was approved by the Institutional Ethics Committee and conducted in accordance with the principles of the Declaration of Helsinki.

Of the 72 patients, 19 were using sitagliptin. Three patients among sitagliptin users and 11 patients among those who were not on sitagliptin treatment were excluded because of refusing to participate the study.

Of the remaining 58 patients, 16 were using sitagliptin [sitagliptin (+)] for glycemic control and 42 were using oral medications for various underlying diseases [sitagliptin (-)]. Seven of 16 sitagliptin users were using sitagliptin for diabetes mellitus. Although the other 9 patients were not diagnosed with diabetes, they had high blood sugar due to drugs such as steroids. Metformin was not preferred due to the risk of lactic acidosis due to drug-related blood sugar elevation in other patients, and sitagliptin was started instead with the recommendation of endocrinology department. The information was collected from the medical records of the patients. Clinical recovery duration and viral clearance were defined as study outcomes.

Current COVID-19 guideline of Ministry of Health in XXX recommends to start hydroxychloroquine (2 x 200 mg) on admittance and continue for five days for the treatment of COVID-19 cases with uncomplicated or mild pneumonia. The same guideline recommends favipiravir (2 x 1600 mg for induction, 2 x 600 mg for maintenance) for five days in patients with severe pneumoniae, if clinical symptoms worsen or pneumonia findings progress despite hydroxychloroquine treatment. Azithromycin or oseltamivir were added when suspected of atypical pneumoniae or influenzae.

Microbiological Diagnosis and Confirmation of Viral Clearance

The combined nasopharyngeal + oropharyngeal swab samples were obtained from the patients by using alginate swabs and transported to the Central Molecular Microbiology Laboratory in a commercially available viral nucleic acid transport medium (BioSpeedy vNAT, Bioeksen, xxx). PCR was performed by using the BioSpeedy COVID-19 RT-qPCR kit (Bioeksen, xxx) and Rotor-Gene Q Real-Time PCR Cycler (Qiagen, xxx) according to the manufacturer's instructions.

The COVID-19 guideline of MoH recommends to show two consecutive negative PCR tests for discharge, thus PCR test was performed on every other day beginning form day three. Viral clearance is confirmed by two consecutive negative PCR tests. However, the day of the first

negative result is considered as the viral clearance day for the survival analysis.

Molecular Docking

ACE2 (1R42)[10] and SARS-CoV-2 spike receptor-binding domain bound with ACE2 (6M0J) [11] proteins were obtained from the protein data bank (PDB) and prepared for docking calculations using Chimera software Version 1.14[12] energy minimization was made by using Open Babel[13] module in the PyRx program[14], before molecular docking calculations. Prepared protein models and sitagliptin ligand were converted to the PDBQT format with default parameters at the PyRx program and then blind docking calculations were made with AutoDock-Vina software[15]. Based on the calculations, nine conformations with the highest affinity energy were taken for further evaluation. Discovery Studio academic version was used to prepare the visuals and make additional calculations[16].

Statistical Analysis

Mean, standard deviation, median and interquartile range (IQR) with 95% confidence interval (CI) were given as descriptive statistics. Shapiro-Wilk test was used to test normality of the continuous variables. The differences between two groups in terms of categorical variables were compared by using Chi-Square test or Fisher's exact test, where appropriate. Mann-Whitney U test was used to test the difference between two groups for non-normally distributed continuous variables. The survival estimations were performed using the method of Kaplan-Meier algorithm, and the comparison between the groups was done with Log-rank test. Cox proportional hazard model was used to estimate the effect of treatment on clinical recovery and viral clearance after adjustment for other variables (age, sex, positive computed tomography findings, lymphocyte count, underlying diseases, and symptom duration). The hazard ratio (HR) and its 95% confidence intervals were calculated. The proportional hazards assumption was evaluated using both statistical test and graphical diagnostics based on the scaled Schoenfeld residuals. Overall evaluation of the Cox proportional hazard model was performed by likelihood ratio test and the significance of coefficients obtained from Cox proportional hazard model was assessed by Wald statistic. Sensitivity analysis was done to check if there is any difference in Cox proportional hazard model before and after adjustment for baseline characteristics. Additional sensitivity analysis was performed to assess the impact of normality assumption for the continuous baseline characteristics. The Bonferroni correction was applied to control Type I error rate. P value less than 0.05 was considered significant.

RESULTS

Basic characteristics and laboratory findings of the two groups on admission are shown on Table 1.

The patients were admitted with fever [49/58 (84.4%)], cough [41/58 (70.6%)], fatigue [35/58 (60.3%)], shortness of breath [32/58 (55.1%)], myalgia/arthralgia [29/58 (50%)], headache [21/58 (36.2%)], sore throat [20/58 (34.4%)], diarrhea [15/58 (25.8%)], pleuritic pain [12/58 (20.6%)], chills [6/58 (10.3%)], nausea and vomiting [5/58 (8.6%)] and nasal congestion [3/58 (5.1%)].

There was no case that was severe at the time of initial diagnosis and hospitalization. The cases were mild and moderate cases. We did not perform clinical grouping as we aimed to evaluate the effect of the sitagliptin on disease progression independently the severity of the patient's clinical status at the beginning.

Mean symptom duration on admission was 4.50 ± 0.81 days in sitagliptin (+) group and 3.90 ± 0.46 days in sitagliptin (-) group. All patients received hydroxychloroquine in accordance with the national guideline. As a result of early clinical recovery, favipiravir was required for only 1 (6.2%) patient in sitagliptin (+) group, whereas 11 (26.1%) patients in sitagliptin (-) group received favipiravir.

Clinical improvement was significantly faster in sitagliptin (+) group. Complete clinical recovery (resolution of all symptoms) was achieved on a mean ± standard error (SE) of 2.50 ± 0.40 days in sitagliptin (+) group and 5.69 ± 0.61 days in sitagliptin (-) group (Log-rank test, $p< 0.001$) (Figure 1).

Table 1. Characteristics and laboratory findings of the subjects on admission

	Sitagliptin (-) (n= 42)	Sitagliptin (+) (n= 16)	p
Age (years)	52.1 ± 16.6 50.5 (23.3)	49.3 ± 14.1 52.0 (24.5)	0.632
Sex, n (%)			0.133
Female	17 (40.5)	10 (62.5)	
Male	25 (59.5)	6 (37.5)	
Underlying diseases, n (%)			
Diabetes mellitus	5 (11.9)	7 (43.8)	0.007
Hypertension	12 (28.6)	6 (37.5)	0.538
COPD	5 (11.9)	1 (6.3)	1.000
Immunosuppression	7 (16.7)	1 (6.3)	0.423
Positive computed tomography findings, n (%)	28 (66.7)	12 (75.0)	0.752
Systolic blood pressure (mmHg)	111.9 ± 7.9 110 (6.3)	118.8 ± 12.7 120 (20)	0.052
Diastolic blood pressure (mmHg)	70.8 ± 6.3 70 (10)	74.4 ± 12.5 70 (22.5)	0.844
Lymphocyte count (10^6/ml; Day 0)	1.46 ± 0.87 1.28 (1.42)	1.59 ± 0.73 1.66 (1.25)	0.509
CRP level (mg/L; Day 0)	25.9 ± 34.3 17.1 (23.8)	28.3 ± 43.6 10.6 (31.1)	0.924
Ferritin (ng/ml; Day 0)	458.9 ± 1336.7 68 (193)	76.8 ± 52.3 68 (77)	0.273
D-dimer (ng/ml; Day 0)	988.2 ± 2952.4 293.0 (347.0)	237.7 ± 158.9 166.0 (254.0)	0.561
HbA1c (Day 0) %	6.4 ± 0.7 6.3 (1.1)	6.9 ± 1.4 6.7 (1.3)	0.367
Patients transferred to ICU, n (%)	7 (16.7)	0 (0.0)	0.173
Death, n (%)	3 (7.1)	0 (0.0)	0.554

Data were given mean ± standard deviation, with the median (IQR) or number of patients with percentage in parentheses.
COPD: Chronic obstructive pulmonary disease, ICU: Intensive care unit.

After adjustment for age, sex, positive computed tomography findings, lymphocyte count, underlying diseases, and symptom duration, there was statistically significant difference in favor of sitagliptin (+) over sitagliptin (-) in terms of clinical improvement (Adjusted HR= 5.669, 95% CI= 2.545-12.628, p< 0.001; crude HR= 3.147, 95% CI= 1.655-5.983, p< 0.001; proportional hazards assumptions were met, p= 0.984, Schoenfeld test).

Change in the laboratory parameters on days three, five, and seven in reference to day zero are given on Table 2. When compared to patients in sitagliptin (-) group, lymphocyte counts on 3rd, 5th and 7th days were significantly higher in patients in sitagliptin (+) group.

PCR tests for SARS-CoV-2 resulted negative in mean (± SE) of 7.50 ± 0.98 days in sitagliptin (+) and 13.17 ± 1.07 days in sitagliptin (-) group, (Figure 2) (Log-rank test, p= 0.003). After adjustment for age, sex, positive computed tomography findings, lymphocyte count, underlying diseases, and symptom duration, there was statistically significant difference in favor of sitagliptin (+) over sitagliptin (-) in terms of viral clearance (Adjusted HR= 2.843, 95% CI= 1.201-6.730, p= 0.017; crude HR= 2.626, 95% CI= 1.318-5.233, p= 0.010; proportional hazards assumptions were met, p= 0.938, Schoenfeld test).

In addition to clinical observations, molecular docking studies were performed. These studies showed that sitagliptin interacts with both ACE2

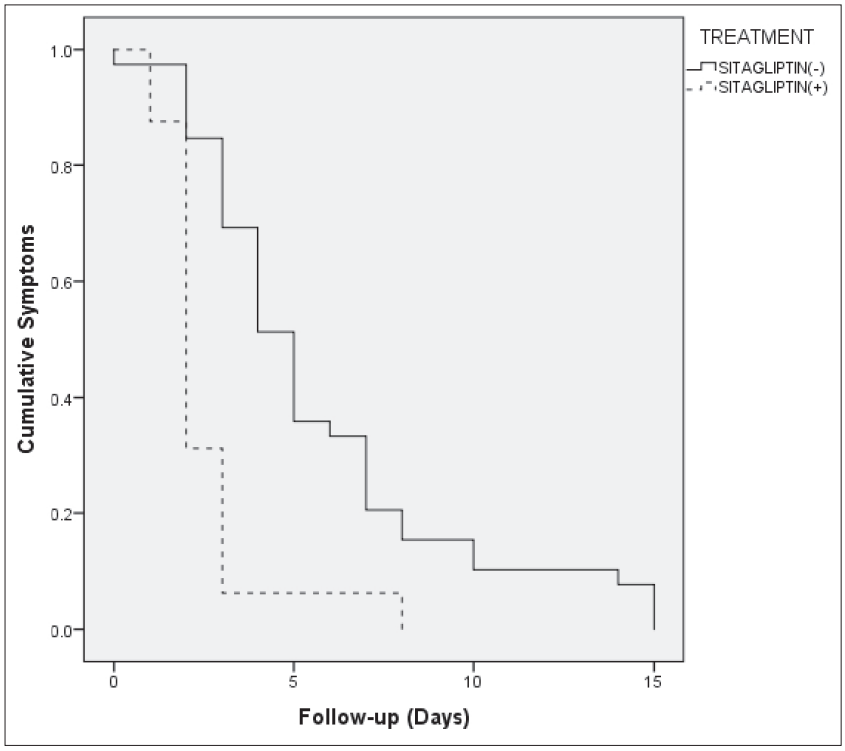

Figure 1. The Kaplan Meier estimate of clinical improvement in sitagliptin (+) and sitagliptin (-) group.

(Figure 3A) and ACE2-bound spike protein of SARS-CoV-2 (Figure 3B).

The binding energy between sitagliptin and ACE2 was calculated as -8.3 kcaL/mol. It is interesting that this energy drops by 0.9 kcL/mol and results in -9.2 kcaL/mol when the virus is attached to ACE2, suggesting that through additional regions, sitagliptin still keeps attached to ACE2. For example, whereas sitagliptin binds through van der Waals and Pi Alkyl to PHE= 40 of ACE2, additional Carbon-H bonds occur when the virus is attached to ACE2 (Table 3).

DISCUSSION

A significantly faster resolution of clinical symptoms was observed in patients that were on sitagliptin treatment. Recently, a retrospective multicenter study in Italy has reported nearly 50% reduction in mortality with the addition of sitagliptin to the standard of treatment in diabetic patients[17]. In this particular study, C-reactive protein at baseline was significantly lower in those assigned to receive sitagliptin and the comparability of the subgroups for baseline conditions was therefore questioned[18]. Another study has examined the associations of baseline conditions such as co-morbidities, treatments, laboratory findings, and clinical outcomes of patients with and without type 2 diabetes[19]. In patients with diabetes, there were trends for an association of DPP4 inhibitor treatment with less severe inflammatory markers. Moreover, the authors have reported that patients treated with DPP4 had better clinical outcomes based on a small number patients (mortality in one out of 11 patients treated with DPP4 inhibitors vs 37 out of 79 patients not receiving DPP4 inhibitor). Thus, randomized, placebo-controlled trials seem to be necessary to confirm the effects of DPP4 inhibitors in patients with diabetes and COVID-19. In a recent multicenter, retrospective cohort study, the effect of pre-existing treatment with DPP4 inhibitors on COVID-19 clinical outcome has been investigated with 9100 patients data using DPP4 inhibitors or other glucose-lowering drugs, and mortality rate has been found statistically significantly lower in the DDP4 inhibitor group[20]. Also, a Phase 3 clinical trial –[The Effect of

Table 2. Change in laboratory variables in reference to day 0

	Sitagliptin (-) n= 42 Median (IQR) 95% CI	Sitagliptin (+) n= 16 Median (IQR) 95% CI	p
Lymphocyte count (x 10^6/ml)			
Day 3-Day 0	-0.045 (0.660) (-0.195-0.150)	0.425 (0.790) (0.130-0.865)	0.004
Day 5-Day 0	0.005 (0.700) (-0.125-0.140)	0.805 (0.390) (0.620-0.950)	< 0.001
Day 7-Day 0	0.035 (0.740) (-0.110-0.245)	0.985 (0.990) (0.553-1.400)	< 0.001
CRP level (mg/L)			
Day 3-Day 0	0.45 (19.43) (-0.50-4.45)	-2.95 (13.85) (-12.90- -0.65)	0.001
Day 5-Day 0	1.40 (13.73) (-0.30-6.15)	-4.95 (23.78) (-21.00- -1.50)	0.001
Day 7-Day 0	1.60 (27.00) (-1.49-8.70)	-7.00 (27.23) (-26.00- -1.85)	0.001
Ferritin (ng/ml)			
Day 3-Day 0	2.00 (37.00) (0.00-10.00)	-10.50 (30.25) (-30.00- -4.00)	0.020
Day 5-Day 0	4.50 (50.58) (0.00-18.00)	-21.00 (38.75) (-42.00- -10.00)	0.004
Day 7-Day 0	20.50 (114.75) (5.00-85.00)	-26.00 (53.95) (-50.00- -13.00)	0.001
D-Dimer (ng/mL)			
Day 3-Day 0	10.00 (91.00) (-7.00-43.00)	-56.50 (97.00) (-121.00- -33.00)	< 0.001
Day 5-Day 0	31.00 (217.00) (-9.00-81.00)	-86.00 (132.25) (-180.00- -59.00)	< 0.001
Day 7-Day 0	27.50 (314.75) (-15.36-215.00)	-107.00 (212.25) (-200.00- -62.00)	< 0.001

Sitagliptin Treatment in COVID-19 Positive Diabetic Patients (SIDIACO)]- has been registered by University of Milan based on the modulatory effect of sitagliptin on pro-inflammatory cytokines, growth factors and vasoactive peptides in the respiratory tract although no patients have been recruited as of today[21].

The mechanism of beneficial effects of sitagliptin, a drug indicated for diabetes and poor glycemic control, is unknown. Based on currently available data, older adults and people of any age who have serious underlying medical conditions including diabetes might be at higher risk for severe illness from SARS-CoV-2 infection[22]. One of the ongoing discussions around available drugs repurposed for COVID-19 concerns DPP4 inhibitors primarily based on, but not limited to, in silico approaches assessing the potential interactions between viral/host protein(s) and drugs in question[23]. Apart from these studies that analyzed the role of DPP4 inhibitors in the transmission of viral infection, a population-based study showed that they suppress T cell proliferation and production of pro-inflammatory cytokines in patients with diabetes[24]. In an experimental model of acute respiratory distress syndrome, the deadliest complication of COVID-19, sitagliptin ameliorated the histological findings of lung damage

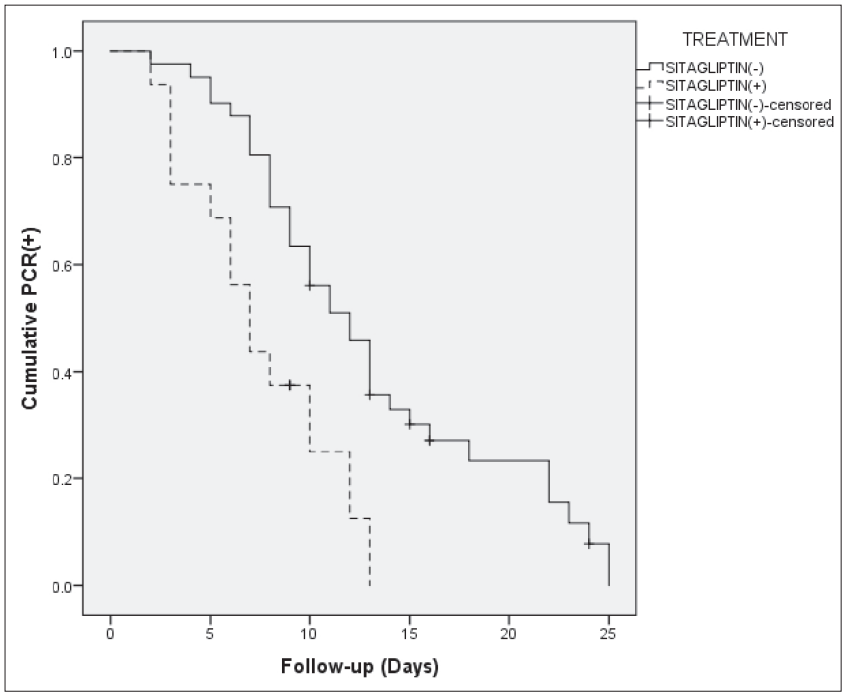

Figure 2. The Kaplan Meier estimate of PCR test negativity in sitagliptin (+) and sitagliptin (-) groups.

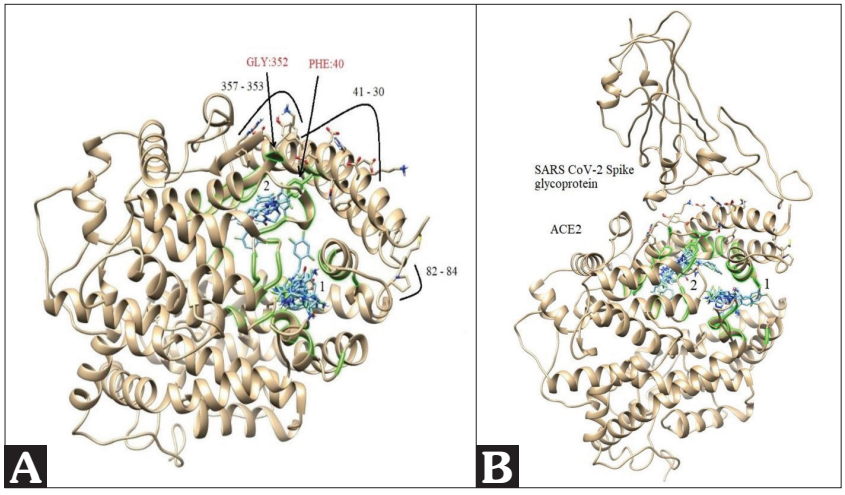

Figure 3. A representation of the interactions between sitagliptin and ACE2 **(A)** and ACE2-bound spike protein of SARS-CoV-2 **(B)**. Sitagliptin interacts with ACE2 on two sites, labeled 1 and 2 on both figures.

and inhibited pro-inflammatory cytokines IL-1β, TNFα and IL-6[25]. In addition, DPP4 knockout mice or treatment of wild types with sitagliptin were shown to be less prone to anti- bleomycin-induced pulmonary and dermal fibrosis[26].

The pathophysiology of severe SARS-CoV-2-induced acute respiratory distress syndrome is known to result in cytokine storm that is characterized by the overproduction of pro-inflammatory cytokines such as TNFα, IL-6, and IL-1β and lead to multiorgan failure[27]. Thus, suppression of pro-inflammatory cytokine overproduction may add to the aforementioned effects of DPP4 inhibitors in SARS-CoV-2 infection.

Table 3. The affinity energies and interactions of sitagliptin on ACE2 and SARS-CoV-2 Spike-bound ACE2

Binding Energy ΔG, kcal/mol				Total Interaction Type*							
No.	ACE2	No.	SARS-CoV-2 Spike-ACE2	Hydrogen		Hydrophobic		Halogen		Favorable	
Area 1											
1	-8.3	1	-9.2	6	4	-	1	8	5	13	8
5	-8.1	2	-8.7	6	3	3	2	6	3	12	8
6	-8.0	3	-8.5	8	2	1	1	6	3	13	5
7	-8.0	6	-8.4	4	4	2	1	7	6	11	11
8	-8.0			6		3		7		14	
9	-8.0			6		2		8		14	
Area 2											
2	-8.2	4	-8.4	4	4	2	3	3	6	8	13
3	-8.2	5	-8.4	3	4	2	2	3	1	7	7
4	-8.1	7	-8.2	6	5	4	2	10	3	17	10
		8	-8.1		5		1		3		9
		9	-8.1		5		2		9		14

Low levels of circulating lymphocyte counts have earlier been reported in most COVID-19 cases and suggested to have prognostic potential as the cardinal laboratory finding in addition to predicting the prognosis of the patients[28]. Therefore, a prompt increase in lymphocyte counts in patients on sitagliptin indicates a faster recovery of host immune system.

High levels of CRP, serum ferritin and D-dimer have been linked to acute respiratory distress syndrome related to COVID-19[29]. Although the levels of CRP, ferritin and D-dimer were similar in both groups on admission, a gradual reduction in these parameters starting within three days in sitagliptin (+) group in addition to the increase in lymphocyte counts ruled out dismal prognosis in these patients at the very beginning of their hospital stay. Indeed, none of our patients in sitagliptin (+) group required intensive care whereas three patients from sitagliptin (-) group had to be transferred to the ICU and eventually died.

Our molecular docking studies showed that sitagliptin has an affinity for both ACE2 and ACE2-bound SARS-CoV-2 spike protein. Although speculative, this may suggest that sitagliptin -through binding the virus and/or antagonizing ACE2- prevents viral entry. This will add to the reported concept of DPP4 being a co-receptor for SARS-CoV-2.

The dynamic profile of SARS-CoV-2 viral load after onset of symptoms is acknowledged. The period between the occurrence of symptoms and a negative SARS-CoV-2 RT-PCR result of a variety of specimens has been documented to be between 6-24 days[30]. Similarly, using specimens from nasopharyngeal and oropharyngeal swabs, the RT-PCR tests resulted negative between 2-25 days in our cohort. Strikingly, viral clearance was obtained in an average of seven and 12 days in sitagliptin users and non-users, respectively and the difference was statistically significant. This is perhaps one of the most important observations of this study indicating that although the presence of sitagliptin may not prevent viral infection or development of the disease state, it does fasten viral clearance and thereby prevent dissemination among the population.

In conclusion, we believe that our results suggested sitagliptin, a member of DPP4 inhibitors, seem to have the potential to be considered for the treatment of COVID-19. Considering the very low risk of hypoglycemia, DPP4 inhibitors may be used safely in even patients without diabetes, additional studies may show the beneficial effects of DPP4 inhibitors in different populations.

ETHICS COMMITTEE APPROVAL

This study was approved by the Ankara University Faculty of Medicine Human Research Ethics Committee (Date: 29.05.2020, Decision No: İ5-294-20).

CONFLICT of INTEREST

None of the authors had conflict of interest.

AUTHORSHIP CONTRIBUTIONS

Concept and Design: GÇ, SCY, AA, KOM

Analysis/Interpretation: GÇ, SCY, AHE, EG, ÖD, KOM, MSB, HN, AA

Data Collection or Processing: GÇ, SCY, İAK, MAÜ, ÖD, KOM, MSB, ZCK, HN, EE

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