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.

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Review

COVID-19 and diabetes; Possible role of polymorphism and rise of telemedicine

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ABSTRACT

Background: Diabetes has been found to be one of the leading comorbidities associated with fatality in COVID-19 patients. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) entry is facilitated by interaction with Angiotensin Converting Enzyme-2 (ACE2) and possible polymorphisms in ACE2 can be a determining factor in host-viral protein interaction. A significant shift of healthcare towards 'Telemedicine' is also on the rise. In this review, the possible effects of ACE2 polymorphisms on SARS-CoV-2 entry along with the escalation of 'telemedicine' is discussed.
Method: An expansive literature search using keywords: "COVID-19", "SARS-CoV-2", "diabetes", "type 2 diabetes", "type 1 diabetes", "ACE2", "polymorphism", "DPP4" and "telemedicine" was conducted on Pubmed and EMBASE till 7th August 2020.
Result: Possible polymorphisms in ACE2 gene can play a role in influencing the virus entry in host body. Telemedicine can bring a new revolution for medical sector.
Conclusion: COVID-19 severity is more heinous among diabetic population. So far, the *in-silico* studies involving human ACE2-viral Spike (S) interaction showed inconsistent predictions regarding some SNPs. But without actual in-vivo studies, a holistic understanding can't be established.

Contents

Abbreviations: COVID-19, Corona virus disease 2019; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; ACE2, Angiotensin Converting Enzyme-2; DM, Diabetes Mellitus; SARS-CoV, Severe acute respiratory syndrome coronavirus; MERS-CoV, Middle East respiratory syndrome coronavirus; SARS, Severe acute respiratory syndrome; MERS, Middle East respiratory syndrome; CFR, Case-fatality rate; T2D, Type 2 diabetes; S, Spike; RBD, Receptor-binding domain; ACE, Angiotensin-converting enzyme; ACEI, ACE inhibitor; ARB, Angiotensin receptor antagonists; SNP, Single nucleotide polymorphism; DPP4, Dipeptidyl peptidase 4; CD26, Cluster of differentiation 26; hDPP4, Human receptordipeptidyl peptidase 4; GLP-1, Glucagon like peptide 1; T1D, Type 1 diabetes; TEDDY, The Environmental Determinants of Diabetes in the Young; H1N1, Influenza A; CORONADO, Coronavirus SARS-CoV2 and Diabetes Outcomes; ISPAD, International Society for Pediatric and Adolescent Diabetes; HbA1c, Glycated hemoglobin; DKA, Diabetes ketoacidosis; SDCC, Steno Diabetes Center Copenhagen.

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1. Introduction

The pandemic corona virus disease 2019 (COVID-19) which originated from Wuhan, China is caused by a single-stranded, positive-sense RNA genome containing enveloped virus [1,2]. Till 6th August 2020, globally 18614177 people have been infected with an unprecedented mortality of 702642 [3]. Diabetes, one of the biggest leading causes of death world-wide with approximately 463 million patient burden, is a metabolic disorder caused by insulin deficiency and/or insulin resistance characterized by hyperglycemia, polyphagia and polydipsia [4,5]. According to clinical manifestations reported from different epidemiological studies, diabetes mellitus (DM) is one of the top comorbidities of COVID-19 patients [6–10].

Severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) share approximately 80% and 50% genetic similarities with Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), respectively [[11], 01]. During Severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) outbreaks, similar vulnerabilities among diabetic patients were also observed. [11, 01].

The Angiotensin Converting Enzyme-2 (ACE2) is the host receptor for SARS-CoV-2 entry. *In-silico* studies have found some single nucleotide polymorphisms (SNPs) which can influence the host-viral interplay. In this review, the possible polymorphisms involved in susceptibility or resistance towards viral entry along with rise of telemedicine are investigated.

2. Mortality and morbidity among COVID-19 patients with existing diabetes

From a summarized report of 72,314 cases in China, the overall case-fatality rate (CFR) was 2.3% (1023 deaths among 44,672 confirmed cases) but CFR was upraised with preexisting comorbidities such as cardiovascular disease (10.5%), diabetes (7.3%), chronic respiratory disease (6.3%), hypertension (6.0%) and cancer (5.6%) [8]. Another study comprising of 1590 Chinese COVID-19 patients found correlation among disease severity with comorbidities where 8.2% of the study participants had two or more coexisting comorbidities. This study also reported symptoms like fever, nasal congestion, productive cough, fatigue, headache to be more prevalent among the COVID-19 patients with existing DM compared to their non-DM, COVID-19 counterparts [12].

In contrast to the high prevalence of DM comorbidity in Chinese population, a study consisting of 1420 patients from 18 different European hospitals showed a much lower prevalence of DM comorbidity (1.7%) [13]. In a study conducted in Iran with 2968 COVID-19 patients, 323 (10.89%) patients had chronic underlying diseases among which diabetes (3.81%) was the most prevalent one. Similar to the Chinese studies, existing comorbidities were also linked significantly with increased mortality in Iranian population [14]. In another study comprising of 1122 COVID-19 patients in 88 U.S. hospitals, 38.5% were found to have either diabetes or uncontrolled hyperglycemia. In that combined group, a more than four times higher mortality rate was observed compared to their respective counterparts without diabetes or uncontrolled hyperglycemia [9]. Another study performed among 305 COVID-19 patients in Georgia, USA also listed diabetes as the top existing comorbidity (39.7%) [15]. A study from Israel with 162 patients had a 19% prior diabetes cases [16]. Another population study in England showed a 31.4% mortality rate for type 2 diabetes (T2D) patients suffering from COVID-19 infection [17].

All these studies conducted in different global parts show a greater risk of mortality among COVID-19 patients with existing diabetes.

3. Possible mechanisms of SARS-CoV-2 entry

In a complicated multifaceted virus- host cell fusion process, viral Spike (S) protein facilitates concurrent receptor binding on the host cell membrane via the receptor-binding domain (RBD) in the S1 subunit and membrane fusion through the S2 subunit [18,19]. ACE2, the cellular receptor for SARS-CoV-2 is augmentedly expressed in alveolar AT2 cells, myocardium, kidney, and pancreas [20–22]. After binding to ACE2, S protein priming and cleavage of the spike are expedited by serine proteases and are followed by successive release of the spike fusion peptide and virus entry through an endosomal pathway [18,19].The low pH and presence of proteases (eg: Cathepsin-L) facilitate the delivery of SARS-CoV-2 genome into the cytosol where further viral replication takes place [23].

Activation of pro-inflammatory cytokines is triggered after the infected cells suffer from apoptosis or necrosis [24]. SARS-CoV-2 infects circulating immune cells and lymphocytopenia is observed which is associated with the degree of SARS-CoV-2 infection severity [6,25,26]. Lack of lymphocytes relieves the restrain on innate immune system leading to “cytokine storm”, a phenomenon which is also known as a rapid increase of high amount of inflammatory cytokines [27]. There is a possibility that hyper-inflammation caused by elevated cytokines in the “cytokine storm” may result in multi-organ failure in SARS-CoV-2 patients [28–30]. Drastic reduction of T cells, CD4 + T and CD8 + T cells and functional exhaustion of remaining T cells are found to be negatively correlated to levels of TNF-α, IL-6 and IL-10, respectively [31]. Exaggerated increase of pro-inflammatory cytokines along with decrease of T cells may be one of the causes of exacerbation of disease severity in COVID-19 patients. Population-studies have also strongly linked pro-inflammatory markers (TNF- α, IL-6, IL-1β, Leptin) with diabetes [32]. Utilizing a phenome-wide Mendelian randomization study, Rao et al. [33] found diabetes to be causally associated with increased lung ACE2 expression. Another study found increased circulating protease Furin in diabetic patients which is involved in facilitating viral entry by cleaving the S1 and S2 domain [34]. So, increased viral entry via increased ACE2 expression and circulating proteases, lymphocytopenia and concurrent increase of inflammatory cytokines can exacerbate SARS-CoV-2 infection in patients with diabetes [23].

4. The perplexity regarding ACE2

Angiotensin-converting enzyme (ACE) converts angiotensin I to angiotensin II. Angiotensin II, a powerful vasoconstrictor causes insulin resistance, endothelial dysfunction, proteinuria, and elevated blood pressure when present at increased level. ACE2 converts angiotensin II into angiotensin 1–7. ACE inhibitors (ACEIs) inhibit the formation of angiotensin II from angiotensin I, followed by conversion of angiotensin I to angiotensin 1–9 which ultimately is transformed to angiotensin 1–7 by ACE2 [35–38]. By binding to the angiotensin receptor themselves, Angiotensin receptor antagonists (ARBs) impede the effect of angiotensin II.

Unbound Angiotensin II rapidly is transmuted to angiotensin 1–7 by increased ACE2 [39]. Angiotensin 1–7 lowers glucose, causes vasodilation and reduces oxidative stress [35,37,38]. Diabetic patients on medication with abovementioned drugs with their elevated ACE2 expression can be susceptible to facilitated SARS-CoV-2 entry, leading to increased chances of disease severity. So, whether COVID-19 patients suffering from diabetes should take abovementioned drugs to control their glycemic level is a phenomenon that needs more exhaustive research.

5. ACE2 polymorphism and relation to COVID-19

The ACE2 gene spanning 39.98 kb of genomic DNA is located at position Xp22.2 [40]. Different population studies reported various ACE2 polymorphisms to be risk associated with diabetes and hypertension. In a study conducted on 503 Caucasian diabetic subjects, rs464188 and rs4240157 SNPs were found to be associated with hypertension in both men and women cohort [41]. In another study in Uyghur population, 8 SNPs (rs1978124, rs2048683, rs2074192, rs233575, rs4240157, rs4646156, rs4646188 and rs879922) were found to be associated with T2D with SNP rs879922 as a possible common genetic loci for T2D and T2D related cardiovascular risks [42]. Genetic variant studies conducted within Chinese ethnicity found comorbidity associated several ACE2 polymorphisms (rs2285666, rs4646188, rs2074192, rs4240157, rs4830542, rs879922) [43–45]. It is a possibility that non-synonymous ACE2 polymorphisms can be impactful on controlling viral entry in host cells via influencing the interaction between ACE2 and S1 proteins. There are amino acid substitutions that can either accelerate or impede the detectability of ACE2 by the viruses [46–48].

Darbani found, 13 variants which can increase interaction between ACE2 and S1 among which H378R and S19 P were Europeans and Africans specific variants, respectively [49]. In the same study, an additional group of 18 SNPs was also found which show some extent of resistance between ACE2-S1 interactions. The Q388 L and M82I were also found as Americans and Africans specific variants, respectively [49]. In a comparative modeling and molecular superimposition analysis study, Hussain et al. found 2 ACE2 alleles, S19 P and E329 G with low binding affinity and lacking some of the key residues in the complex formation with SARS-CoV-2 S protein [50]. It propounds of intrinsic resistance to some extent against the SARS-CoV-2 infection. Othoman et al. mapped 8 rare genetic variants to the interaction surface of ACE2; but none of the variants confer any resistance against the virus entry according to enthalpy and entropy calculation [51]. Some of the variants show dissimilar (D355 N, E37 K, G326E, G352 V, M82I, T27A, E329 G and S19 P) results among the three studies [49–51]. S19 P and E329 G showed totally different interpretations in all three of them. In contrast to the modeling studies which show no effect for D355 N, E329 G, E37 K, G326E, G352 V and M82I mutations on the ACE2-S interaction [51], Darbani introduced them as potential inhibitor genetic variants [49], which have also been confirmed in an in-vivo experiment [48]. Studies exploring the impact of ACE2 polymorphisms are still in nascent phase. All the studies mentioned in table 01 have employed different methods. So, without more comprehensive clinical data, these interpretations should be treated with caution. The likelihood of polymorphisms affecting viral infection has already been observed in case of certain HIV strains. Genetic variants in the CD4 receptor (C868 T) and CCR5-Δ32 have conferred susceptibility and resistance, respectively [52,53]. Some primary results have found and discussed the associations between the ACE2 variants and comorbidities like diabetes [41,42,45]. So, based on such findings, the possibility of ACE2 polymorphisms rendering susceptibility or resistance towards COVID-19 must be scrutinized extensively [41–45,52,53]. Whether the polymorphisms have more pronounced effects among diabetic patients with COVID-19 infection should be taken into consideration while exploring the possible role of viral entry in hosts (Table 1).

6. Role of DPP4

Dipeptidyl peptidase 4 (DPP4) or cluster of differentiation 26 (CD26), is a type II transmembrane glycoprotein expressed ubiquitously in many tissues such as lung, kidney, liver, gut, and immune cells [54]. In MERS-CoV infection, virus entry is mediated through binding RBD of S glycoprotein to human receptor, dipeptidyl peptidase 4(hDPP4) [55]. Mechanisms of degradation of incretins such as glucagon like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide by DPP4 with subsequent reduction in insulin secretion are still not fully comprehensible [56]. Vankadari et al. hypothesized of interaction between DPP4/CD26 with the S1 domain of the S protein of SARS-CoV-2 [57]. This suggests of a supplemental virus-host interaction along with the principal interaction between ACE2 and S proteins. At least seven of the predicted DPP4 residues involved in SARS-CoV-2 interaction are also targeted by the Bat-CoV HKU4 [58], which is phylogenetically correlated to the MERS-CoV. Additional sites (Q286, I287, N338, V341, R336) have been predicted to bind to the S1 domain via van der waals or by hydrogen binding [57]. Kleine-Weber et al. found 4 polymorphisms (K267E, K267 N, A291 P and Δ346-348) which strongly reduce interaction between MERS-CoV S- DPP4 [59]. Unlike ACE2, the exact role of DPP4 in SARS-CoV-2 hasn't been elucidated with substantial results except the *in-silico* approaches. So whether any polymorphisms in DPP4 can govern the host- SARS-CoV-2 interaction- is still unknown. But the likelihood of impact of DPP4 polymorphisms on DPP4-SARS-CoV-2 interaction can't be ruled out with certainty.

7. Covid-19 and type 1 diabetes

T1D (Type 1 diabetes), the autoimmune diabetes entity occurs due to the destruction of beta islet cells following a concurrent insulin depletion and rising hyperglycemia. [60]. Viral infections have been found to trigger an antagonistic immune response leading towards T1D via exacerbated autoimmune insulitis and beta cell destruction. [61]. In a TEDDY (The Environmental Determinants of Diabetes in the Young) study conducted on 87,327 young participants, respiratory tract infection was correlated with increased risk of islet autoimmunity. [62]. In another open cohort study conducted on 2.5 million Norwegian partakers, a twofold excess of incident T1D was found in the subgroup of laboratory-confirmed pandemic influenza A (H1N1) [63]. These studies suggest of possible connections between T1D and viral respiratory infection. So far, there exists only a few investigative studies between T1D and COVID-19 infection. A wide-range study in England recorded 1.5% deaths of T1D patients among a total of 23,804 COVID-19 deaths. There was a very conspicuous relationship between deprivation and T1D mortality indicated by 29·6% deaths in the most deprived quintile and only 10·4% deaths in the least deprived quintile among T1D patients [17]. In the CORONADO (Coronavirus SARS-CoV2 and Diabetes Outcomes) study, T1D represented 3.0% of the total 1317 diabetic patients with no reported death within T1D group below age 65 [64]. Such low mortality of COVID-19 infection was also reported by International Society for Pediatric and Adolescent Diabetes (ISPAD). In a transversal observation made in Alghero, Sardinia, an Italian county with one of the greatest concentrations of T1D patients in the world, ISPAD reported only 1 case of COVID-19 patient with T1D who also made full easeful recovery [65]. Similar to the TEDDY study, whether COVID-19 infection can exacerbate islet autoimmunity should be investigated further. Till now, the mortality rate of COVID-19 patients with T1D has been reported to be low in the

Table 1
Summary of the possible effects of ACE2 SNPs on SARS-CoV-2 entry.

Reference	SNP	Possible effect on ACE2-viral S interaction	Method of study
[49]	rs73635825 [S19 P], rs778030746 [I21 V], rs1244687367 [I21 T], rs756231991 [E23 K], rs1434130600 [A25 T], rs4646116 [K26R], rs781255386 [T27A], rs778500138 [E35D], rs1199100713 [N64 K], rs867318181 [E75 G], rs763395248 [T92I], rs1395878099 [Q102 P], rs142984500 [H378R])	Increases susceptibility	SNP data was extracted from GenBank, dbSNP, 1000 genomes project, Exome Aggregation Consortium aggregation consortium (ExAC) and Genome Aggregation Database (gnomAD). For every variant, data was processed using chi-square statistics. The abundance of the rare variant and the corresponding reference allele in comparison were used in the chi-square test.
	rs1348114695 [E35 K], rs146676783 [E37 K], rs1192192618 [Y50 F], rs760159085 [N51D], rs1569243690 [N51S], rs1325542104 [M62 V], rs755691167 [K68E], rs1256007252 [F72 V], rs766996587 [M82I], rs759579097 [G326E], rs143936283 [E329 G], rs370610075 [G352 V], rs961360700 [D355 N], rs751572714 [Q388 L], rs762890235 [P389 H], rs1016409802 [H505R], rs1352194082 [R514 G/*], and rs1263424292 [Y515C]	Increases resistance	
[50]	rs73635825 [S19 P], rs143936283 [E329 G]	Increases resistance	Effects of amino acid substitution on protein stability was determined by I-Mutant2 which calculates the free energy changes ($\Delta\Delta G$) in wild type and mutant variants. The functional impact of all selected allelic variants of ACE2 was predicted using sorting intolerant from tolerant (SIFT), Polymorphism Phenotyping v2 (PolyPhen-2), combined annotation-dependent depletion (CADD) and rare exome variant ensemble learner (REVEL).
[51]	rs961360700 [D355 N], rs143936283 [E329 G], rs146676783 [E37 K], rs759579097 [G326E], rs370610075 [G352 V], rs766996587 [M82I], rs73635825 [S19 P], rs781255386 [T27A]	No marginal effect	Variants were extracted from gnomAD and dbSNP. The folding energy changes and interaction energy of the mutant ACE2 were calculated with DynaMut and (PROtein binDIng enerGY prediction) PRODIGY, respectively.

[SNP: Single Nucleotide Polymorphism, ACE2: Angiotensin Converting Enzyme-2, SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2].

stratified studies. Tatti et al. coined a hypothesis that the slight propensity of T1D towards the Th1 inflammatory immunity can be a possible reason for such low infection of COVID-19 among T1D patients [66].

8. Rise of the trend of Telemedicine

One of the mentionable changes seen is the rise of telemedicine which enables the healthcare professionals to provide valid information for diagnosis, treatment and prevention of disease and injuries with help of telecommunication technologies [67]. For a chronic disease like diabetes that requires recurrent physician consultation, telemedicine can be a viable alternative for patients seeking medical guidance without the risk of coronavirus infection [68]. A meta-analysis from China showed a reduction in HbA1c (glycated hemoglobin) by 0.37% ($p < 0.001$) in telemedicine group when compared to controls [69]. Insolvency and inaccessibility of interactive media can be impediments for telemedicine initiatives. But an endeavor in India, in forms of customized mobile van with facility of telemedicine (use of computer and Skype) in underprivileged areas of Delhi has showed success in screening and managing diabetes [70].

In times of this pandemic, from a study comprising of 33 T1D patients from Italy, who shared their data with the diabetes outpatient clinic on a web-based cloud system (LibreView; Abbott Diabetes Care); it was construed that despite the limited possibility to exercise and the corresponding psychological stress of lock-down, glycemic control improved in patients with T1D. This advocates that slowing down routine daily activities can be conducive on T1D management, at least in the short term [71]. Another study conducted on 307 Spanish T1D patients using the FreeStyle Libre FGM system (Abbott Diabetes Care) showed no deterioration in glycemic control [72]. Similar to the Italian study, greater stability in schedules and better self-management were found to be propitious for glycemic control for a transitory period. In another study in Los Angeles, USA, telemedicine facilitated by Clarity Software and the "Share" feature with the use of Dexcom G6 continuous glucose monitoring (CGM) was employed and became successful to manage high-risk patients with T1D and diabetes ketoacidosis (DKA). This study also emphasized the elaborated implication of telemedicine by citing two severe cases of T1D complications (01. a 21 year old male with T1D; 02. 26 years old female with diabetes insipidus) [73]. According to another report conducted on 5000 T1D patients at Steno Diabetes Center Copenhagen (SDCC), telemedicine was proved to be a success and physical visit was only required with the new onsets of T1D or for critical patients [74].

9. Conclusion

From the epidemiological studies of COVID-19 patients around the globe, diabetes can be construed as one of the top comorbidities to aggravate the infection but the actual percentage of COVID-19 patients with T1D and T2D are not clear. In T2D patients with this infection, pathogenicity mechanism revolving around ACE2 needs more elucidation. Whether polymorphic variants in ACE2 can contribute to susceptibility or resistance for SARS-Cov-2 infection and more importantly the implications of these variants with diabetes are still obscured. The relationship between T1D and COVID-19 also commands in-depth exploration. Due to this lock-down, a rise in telemedicine has also been observed which can be a revolutionary step in diabetes care where elderly or critical patients can easily get access to the proper care promptly.

Conflicts of interest

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Data availability

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Contribution statement

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