# Evidence Search Service Results of your search request

## ACE 2 levels in Diabetes, Hypertension, ACE inhibitors and/or ARBs

**ID of request:** 22305  
**Date of request:** 16th March, 2020  
**Date of completion:** 19th March, 2020

If you would like to request any articles or any further help, please contact:  Lisa Mason at [Lisa.Mason@geh.nhs.uk](mailto:Lisa.Mason@geh.nhs.uk)

Please acknowledge this work in any resulting paper or presentation as: Evidence search: ACE 2 levels in Diabetes, Hypertension, ACE inhibitors and/or ARBs. Lisa Mason. (19th March, 2020). NUNEATON, UK: George Eliot Hospital William Harvey Library.

**Sources searched**  
Journal of Hypertension (1)  
MEDLINE (20)  
PubMed (3)  
The Renal Association, UK (1)

**Date range used** (5 years, 10 years): All   
**Limits used** (gender, article/study type, etc.): Human   
**Search terms and notes** (full search strategy for database searches below):

MEDLINE and EMBASE- see strategies below

Google scholar

NICE evidence

Strategy 826050

|  |  |  |  |
| --- | --- | --- | --- |
| **#** | **Database** | **Search term** | **Results** |
| 2 | Medline | ("ACE 2" OR "Angiotensin converting enzyme 2").ti,ab | 1314 |
| 3 | Medline | exp HYPERTENSION/ | 279732 |
| 4 | Medline | exp "DIABETES MELLITUS"/ | 415957 |
| 5 | Medline | exp "ANGIOTENSIN-CONVERTING ENZYME INHIBITORS"/ | 43155 |
| 6 | Medline | exp "ANGIOTENSIN RECEPTOR ANTAGONISTS"/ | 23265 |
| 7 | Medline | (3 OR 4 OR 5 OR 6) | 703266 |
| 8 | Medline | (2 AND 7) | 421 |
| 9 | Medline | 8 [Humans] | 194 |
| 10 | Medline | (level OR levels).ti,ab | 3870884 |
| 11 | Medline | (8 AND 10) | 196 |
| 12 | Medline | 11 [Humans] | 68 |
| 13 | Medline | (2 AND 5) | 115 |
| 14 | Medline | (2 AND 5) [Humans] | 56 |
| 15 | Medline | (coronavirus OR COVID-19).ti,ab | 10379 |
| 16 | Medline | (5 AND 15) | 4 |
| 17 | Medline | (2 AND 15) | 177 |
| 18 | Medline | (2 AND 5) | 115 |
| 19 | Medline | 18 [Humans] | 56 |
| 21 | EMBASE | \*"DIPEPTIDYL CARBOXYPEPTIDASE INHIBITOR"/ | 22994 |
| 22 | EMBASE | (ace 2).ti,ab | 421 |
| 23 | EMBASE | exp "ANGIOTENSIN RECEPTOR ANTAGONIST"/ | 89776 |
| 24 | EMBASE | (Angiotensin converting enzyme 2).ti,ab | 1562 |
| 25 | EMBASE | (ACE 2).ti,ab | 421 |
| 26 | EMBASE | (24 OR 25) | 1872 |
| 27 | EMBASE | (21 AND 26) | 35 |
| 28 | EMBASE | exp "DIABETES MELLITUS"/ | 931771 |
| 29 | EMBASE | (covid-19 OR coronavirus).ti,ab | 11070 |
| 30 | EMBASE | (25 AND 28) | 54 |
| 31 | EMBASE | (29 AND 30) | 0 |
| 32 | EMBASE | (28 AND 29) | 81 |
| 33 | Medline | (2 AND 6) | 106 |

Strategy 826098

|  |  |  |  |
| --- | --- | --- | --- |
| **#** | **Database** | **Search term** | **Results** |
| 1 | Medline | exp "DIABETES MELLITUS"/ | 415957 |
| 2 | Medline | exp CORONAVIRUS/ | 11164 |
| 3 | Medline | (1 AND 2) | 8 |
| 4 | Medline | (covid-19).ti,ab | 447 |
| 5 | Medline | (1 AND 4) | 0 |
| 7 | Medline | (diabetes).ti,ab | 501463 |
| 8 | Medline | (1 OR 7) | 629066 |
| 9 | Medline | (4 AND 8) | 5 |
| 10 | Medline | (2 OR 4) | 11692 |
| 11 | Medline | (8 AND 10) | 41 |
| 12 | EMBASE | exp "DIABETES MELLITUS"/ | 932182 |
| 13 | EMBASE | (covid-19 OR coronavirus).ti,ab | 11140 |
| 14 | EMBASE | (12 AND 13) | 83 |
| 15 | EMBASE | exp "SEVERE ACUTE RESPIRATORY SYNDROME"/ OR exp "SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS"/ | 10372 |
| 16 | EMBASE | (12 AND 15) | 129 |

For more information about the resources please go to: <https://geh.wordpress.ptfs-europe.co.uk>.

## Summary of Results

The evidence service from the Centre for Evidence Based Medicine at the University of Oxford are producing a number of evidence summaries on selected topics. The questions under consideration include:

* What is the effect of ACE-I/ARB and pneumonia in Covid-19?
* Should you Stop ACE/ARBs prior to infection?
* Should you add ACE/ARB if you get infected with COVD-19?

We would recommend that you check back on their web pages <https://www.cebm.net/oxford-covid-19/> to pick up the results of these searches

The results included in this report are limited to humans, if you would like the search expanded to include animal subjects, please get in touch.

A number of societies and institutions have responded to the Lancet letter and reports in the press- a google search will show these quickly, however they have mostly not been incuded here as they do not contain any further evidence.

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The Renal Association, UK

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2. [Can angiotensin receptor-blocking drugs perhaps be harmful in the COVID-19 pandemic](#Research610163)
3. [Characteristics of and Public Health Responses to the Coronavirus Disease 2019 Outbreak in China.](#Research608450)
4. [Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China.](#Research608448)
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14. [Prevalence of comorbidities in the Middle East respiratory syndrome coronavirus (MERS-CoV): a systematic review and meta-analysis.](#Research608453)
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## A. Institutional Publications

#### The Renal Association, UK

**The Renal Association, UK position statement on COVID-19 and ACE Inhibitor/Angiotensin Receptor Blocker use** (2020)

The Renal Association

[Available online at this link](https://www.knowledgeshare.nhs.uk/index.php?PageID=link_resolver&link=2002f00d3b7bda58dd4ffa434da4a3f1)

## B. Original Research

1. **Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection?**  
   Fang Lei The Lancet. Respiratory medicine 2020;:No page numbers.

1. **Can angiotensin receptor-blocking drugs perhaps be harmful in the COVID-19 pandemic**  
   Esler Journal of Hypertension 2020;38(1):1-2.

[Available online at this link](https://www.knowledgeshare.nhs.uk/index.php?PageID=link_resolver&link=2267904c85632908eb992c099d1855a6)

1. **Characteristics of and Public Health Responses to the Coronavirus Disease 2019 Outbreak in China.**  
   Deng Sheng-Qun Journal of clinical medicine 2020;9(2):No page numbers.

In December 2019, cases of unidentified pneumonia with a history of exposure in the Huanan Seafood Market were reported in Wuhan, Hubei Province. A novel coronavirus, SARS-CoV-2, was identified to be accountable for this disease. Human-to-human transmission is confirmed, and this disease (named COVID-19 by World Health Organization (WHO)) spread rapidly around the country and the world. As of 18 February 2020, the number of confirmed cases had reached 75,199 with 2009 fatalities. The COVID-19 resulted in a much lower case-fatality rate (about 2.67%) among the confirmed cases, compared with Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS). Among the symptom composition of the 45 fatality cases collected from the released official reports, the top four are fever, cough, short of breath, and chest tightness/pain. The major comorbidities of the fatality cases include hypertension, diabetes, coronary heart disease, cerebral infarction, and chronic bronchitis. The source of the virus and the pathogenesis of this disease are still unconfirmed. No specific therapeutic drug has been found. The Chinese Government has initiated a level-1 public health response to prevent the spread of the disease. Meanwhile, it is also crucial to speed up the development of vaccines and drugs for treatment, which will enable us to defeat COVID-19 as soon as possible.

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[Available online at this link](https://www.knowledgeshare.nhs.uk/index.php?PageID=link_resolver&link=79c6d25914a228809f8b5b4cedf69fc7)

1. **Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China.**  
   Zhang Jin-Jin Allergy 2020;:No page numbers.

BACKGROUNDCoronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has been widely spread. We aim to investigate the clinical characteristic and allergy status of patients infected with SARS-CoV-2.METHODSElectronic medical records including demographics, clinical manifestation, comorbidities, laboratory data, and radiological materials of 140 hospitalized COVID-19 patients, with confirmed result of SARS-CoV-2 viral infection, were extracted and analyzed.RESULTSAn approximately 1:1 ratio of male (50.7%) and female COVID-19 patients was found, with an overall median age of 57.0 years. All patients were community-acquired cases. Fever (91.7%), cough (75.0%), fatigue (75.0%), and gastrointestinal symptoms (39.6%) were the most common clinical manifestations, whereas hypertension (30.0%) and diabetes mellitus (12.1%) were the most common comorbidities. Drug hypersensitivity (11.4%) and urticaria (1.4%) were self-reported by several patients. Asthma or other allergic diseases were not reported by any of the patients. Chronic obstructive pulmonary disease (COPD, 1.4%) patients and current smokers (1.4%) were rare. Bilateral ground-glass or patchy opacity (89.6%) was the most common sign of radiological finding. Lymphopenia (75.4%) and eosinopenia (52.9%) were observed in most patients. Blood eosinophil counts correlate positively with lymphocyte counts in severe (r = .486, P < .001) and nonsevere (r = .469, P < .001) patients after hospital admission. Significantly higher levels of D-dimer, C-reactive protein, and procalcitonin were associated with severe patients compared to nonsevere patients (all P < .001).CONCLUSIONDetailed clinical investigation of 140 hospitalized COVID-19 cases suggests eosinopenia together with lymphopenia may be a potential indicator for diagnosis. Allergic diseases, asthma, and COPD are not risk factors for SARS-CoV-2 infection. Older age, high number of comorbidities, and more prominent laboratory abnormalities were associated with severe patients.

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1. **Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study.**  
   Zhou Fei Lancet (London, England) 2020;:No page numbers.

BACKGROUNDSince December, 2019, Wuhan, China, has experienced an outbreak of coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Epidemiological and clinical characteristics of patients with COVID-19 have been reported but risk factors for mortality and a detailed clinical course of illness, including viral shedding, have not been well described.METHODSIn this retrospective, multicentre cohort study, we included all adult inpatients (≥18 years old) with laboratory-confirmed COVID-19 from Jinyintan Hospital and Wuhan Pulmonary Hospital (Wuhan, China) who had been discharged or had died by Jan 31, 2020. Demographic, clinical, treatment, and laboratory data, including serial samples for viral RNA detection, were extracted from electronic medical records and compared between survivors and non-survivors. We used univariable and multivariable logistic regression methods to explore the risk factors associated with in-hospital death.FINDINGS191 patients (135 from Jinyintan Hospital and 56 from Wuhan Pulmonary Hospital) were included in this study, of whom 137 were discharged and 54 died in hospital. 91 (48%) patients had a comorbidity, with hypertension being the most common (58 [30%] patients), followed by diabetes (36 [19%] patients) and coronary heart disease (15 [8%] patients). Multivariable regression showed increasing odds of in-hospital death associated with older age (odds ratio 1·10, 95% CI 1·03-1·17, per year increase; p=0·0043), higher Sequential Organ Failure Assessment (SOFA) score (5·65, 2·61-12·23; p<0·0001), and d-dimer greater than 1 μg/L (18·42, 2·64-128·55; p=0·0033) on admission. Median duration of viral shedding was 20·0 days (IQR 17·0-24·0) in survivors, but SARS-CoV-2 was detectable until death in non-survivors. The longest observed duration of viral shedding in survivors was 37 days.INTERPRETATIONThe potential risk factors of older age, high SOFA score, and d-dimer greater than 1 μg/L could help clinicians to identify patients with poor prognosis at an early stage. Prolonged viral shedding provides the rationale for a strategy of isolation of infected patients and optimal antiviral interventions in the future.FUNDINGChinese Academy of Medical Sciences Innovation Fund for Medical Sciences; National Science Grant for Distinguished Young Scholars; National Key Research and Development Program of China; The Beijing Science and Technology Project; and Major Projects of National Science and Technology on New Drug Creation and Development.

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1. **Diabetes and COVID-19.**  
   Bloomgarden Zachary T. Journal of diabetes 2020;12(4):347-348.

[Available online at this link](https://www.knowledgeshare.nhs.uk/index.php?PageID=link_resolver&link=f6c49f64333f147567a0e352d00a39b3)

1. **Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China.**  
   Li Bo Clinical research in cardiology : official journal of the German Cardiac Society 2020;:No page numbers.

BACKGROUNDStudies have reminded that cardiovascular metabolic comorbidities made patients more susceptible to suffer 2019 novel corona virus (2019-nCoV) disease (COVID-19), and exacerbated the infection. The aim of this analysis is to determine the association of cardiovascular metabolic diseases with the development of COVID-19.METHODSA meta-analysis of eligible studies that summarized the prevalence of cardiovascular metabolic diseases in COVID-19 and compared the incidences of the comorbidities in ICU/severe and non-ICU/severe patients was performed. Embase and PubMed were searched for relevant studies.RESULTSA total of six studies with 1527 patients were included in this analysis. The proportions of hypertension, cardia-cerebrovascular disease and diabetes in patients with COVID-19 were 17.1%, 16.4% and 9.7%, respectively. The incidences of hypertension, cardia-cerebrovascular diseases and diabetes were about twofolds, threefolds and twofolds, respectively, higher in ICU/severe cases than in their non-ICU/severe counterparts. At least 8.0% patients with COVID-19 suffered the acute cardiac injury. The incidence of acute cardiac injury was about 13 folds higher in ICU/severe patients compared with the non-ICU/severe patients.CONCLUSIONPatients with previous cardiovascular metabolic diseases may face a greater risk of developing into the severe condition and the comorbidities can also greatly affect the prognosis of the COVID-19. On the other hand, COVID-19 can, in turn, aggravate the damage to the heart.

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1. **Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China.**  
   Wu Chaomin JAMA internal medicine 2020;:No page numbers.

ImportanceCoronavirus disease 2019 (COVID-19) is an emerging infectious disease that was first reported in Wuhan, China, and has subsequently spread worldwide. Risk factors for the clinical outcomes of COVID-19 pneumonia have not yet been well delineated.ObjectiveTo describe the clinical characteristics and outcomes in patients with COVID-19 pneumonia who developed acute respiratory distress syndrome (ARDS) or died.Design, Setting, and ParticipantsRetrospective cohort study of 201 patients with confirmed COVID-19 pneumonia admitted to Wuhan Jinyintan Hospital in China between December 25, 2019, and January 26, 2020. The final date of follow-up was February 13, 2020.ExposuresConfirmed COVID-19 pneumonia.Main Outcomes and MeasuresThe development of ARDS and death. Epidemiological, demographic, clinical, laboratory, management, treatment, and outcome data were also collected and analyzed.ResultsOf 201 patients, the median age was 51 years (interquartile range, 43-60 years), and 128 (63.7%) patients were men. Eighty-four patients (41.8%) developed ARDS, and of those 84 patients, 44 (52.4%) died. In those who developed ARDS, compared with those who did not, more patients presented with dyspnea (50 of 84 [59.5%] patients and 30 of 117 [25.6%] patients, respectively [difference, 33.9%; 95% CI, 19.7%-48.1%]) and had comorbidities such as hypertension (23 of 84 [27.4%] patients and 16 of 117 [13.7%] patients, respectively [difference, 13.7%; 95% CI, 1.3%-26.1%]) and diabetes (16 of 84 [19.0%] patients and 6 of 117 [5.1%] patients, respectively [difference, 13.9%; 95% CI, 3.6%-24.2%]). In bivariate Cox regression analysis, risk factors associated with the development of ARDS and progression from ARDS to death included older age (hazard ratio [HR], 3.26; 95% CI 2.08-5.11; and HR, 6.17; 95% CI, 3.26-11.67, respectively), neutrophilia (HR, 1.14; 95% CI, 1.09-1.19; and HR, 1.08; 95% CI, 1.01-1.17, respectively), and organ and coagulation dysfunction (eg, higher lactate dehydrogenase [HR, 1.61; 95% CI, 1.44-1.79; and HR, 1.30; 95% CI, 1.11-1.52, respectively] and D-dimer [HR, 1.03; 95% CI, 1.01-1.04; and HR, 1.02; 95% CI, 1.01-1.04, respectively]). High fever (≥39 °C) was associated with higher likelihood of ARDS development (HR, 1.77; 95% CI, 1.11-2.84) and lower likelihood of death (HR, 0.41; 95% CI, 0.21-0.82). Among patients with ARDS, treatment with methylprednisolone decreased the risk of death (HR, 0.38; 95% CI, 0.20-0.72).Conclusions and RelevanceOlder age was associated with greater risk of development of ARDS and death likely owing to less rigorous immune response. Although high fever was associated with the development of ARDS, it was also associated with better outcomes among patients with ARDS. Moreover, treatment with methylprednisolone may be beneficial for patients who develop ARDS.

1. **Structure analysis of the receptor binding of 2019-nCoV.**  
   Chen Y. Biochemical and biophysical research communications 2020;:No page numbers.

2019-nCoV is a newly identified coronavirus with high similarity to SARS-CoV. We performed a structural analysis of the receptor binding domain (RBD) of spike glycoprotein responsible for entry of coronaviruses into host cells. The RBDs from the two viruses share 72% identity in amino acid sequences, and molecular simulation reveals highly similar ternary structures. However, 2019-nCoV has a distinct loop with flexible glycyl residues replacing rigid prolyl residues in SARS-CoV. Molecular modeling revealed that 2019-nCoV RBD has a stronger interaction with angiotensin converting enzyme 2 (ACE2). A unique phenylalanine F486 in the flexible loop likely plays a major role because its penetration into a deep hydrophobic pocket in ACE2. ACE2 is widely expressed with conserved primary structures throughout the animal kingdom from fish, amphibians, reptiles, birds, to mammals. Structural analysis suggests that ACE2 from these animals can potentially bind RBD of 2019-nCoV, making them all possible natural hosts for the virus. 2019-nCoV is thought to be transmitted through respiratory droplets. However, since ACE2 is predominantly expressed in intestines, testis, and kidney, fecal-oral and other routes of transmission are also possible. Finally, antibodies and small molecular inhibitors that can block the interaction of ACE2 with RBD should be developed to combat the virus.

1. **[Inhibitors of RAS Might Be a Good Choice for the Therapy of COVID-19 Pneumonia].**  
   Sun ML Zhonghua jie he he hu xi za zhi = Zhonghua jiehe he huxi zazhi = Chinese journal of tuberculosis and respiratory diseases 2020;43(3):219-222.

The novel coronavirus 2019 (COVID-19) infected patients by binding human ACE2, leading to severe pneumonia and highly mortality rate in patients. At present, there is no definite and effective treatment for COVID-19. ACE2 plays an important role in the RAS, and the imbalance between ACE/Ang II/AT1R pathway and ACE2/Ang (1-7)/Mas receptor pathway in the RAS system will lead to multi-system inflammation. Increased ACE and Ang II are poor prognostic factors for severe pneumonia. Animal studies have shown that RAS inhibitors could effectively relieve symptoms of acute severe pneumonia and respiratory failure. The binding of COVID-19 and ACE2 resulted in the exhaustion of ACE2, and then ACE2/Ang (1-7)/Mas receptor pathway was inhibited. The balance of the RAS system was broken, and this would lead to the exacerbation of acute severe pneumonia. Therefore, we speculate that ACEI and AT1R inhibitors could be used in patients with COVID-19 pneumonia under the condition of controlling blood pressure, and might reduce the pulmonary inflammatory response and mortality.

1. **A review of urinary angiotensin converting enzyme 2 in diabetes and diabetic nephropathy.**  
   Gilbert Akankwasa Biochemia medica 2019;29(1):010501.

Urinary angiotensin converting enzyme 2 (ACE2) is significantly increased in diabetes and diabetic nephropathy. While studies on its clinical significance are still underway, its urinary expression, association with metabolic and renal parameters has been in the recent past considerably studied. The recent studies have demystified urine ACE2 in many ways and suggested the roles it could play in the management of diabetic nephropathy. In all studies the expression of urinary ACE2 was determined by enzyme activity assay and/with the quantification of ACE2 protein and mRNA by methods whose reliability are yet to be evaluated. This review summarizes recent findings on expression of urinary ACE2, examines its relationship with clinical parameters and highlights possible applications in management of diabetic nephropathy.

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[Available online at this link](https://www.knowledgeshare.nhs.uk/index.php?PageID=link_resolver&link=49e5027e1bd5268f5f343de7601a2c62)

[Available online at this link](https://www.knowledgeshare.nhs.uk/index.php?PageID=link_resolver&link=e35b1b8de43467b9f49fbdb0a6bfcbde)

[Available online at this link](https://www.knowledgeshare.nhs.uk/index.php?PageID=link_resolver&link=fcb66b94178dd7fcb8963250b595a0e9)

1. **Clinical outcomes of current medical approaches for Middle East respiratory syndrome: A systematic review and meta-analysis.**  
   Morra Mostafa Ebraheem Reviews in medical virology 2018;28(3):e1977.

Middle East respiratory syndrome (MERS) is a respiratory disease caused by MERS coronavirus. Because of lack of vaccination, various studies investigated the therapeutic efficacy of antiviral drugs and supportive remedies. A systematic literature search from 10 databases was conducted and screened for relevant articles. Studies reporting information about the treatment of MERS coronavirus infection were extracted and analyzed. Despite receiving treatment with ribavirin plus IFN, the case fatality rate was as high as 71% in the IFN-treatment group and exactly the same in patients who received supportive treatment only. Having chronic renal disease, diabetes mellitus and hypertension increased the risk of mortality (P < .05), and chronic renal disease is the best parameter to predict the mortality. The mean of survival days from onset of illness to death was 46.6 (95% CI, 30.5-62.6) for the IFN group compared with 18.8 (95% CI, 10.3-27.4) for the supportive-only group (P = .001). Delay in starting treatment, older age group, and preexisting comorbidities are associated with worse outcomes. In conclusion, there is no difference between IFN treatment and supportive treatment for MERS patients in terms of mortality. However, ribavirin and IFN combination might have efficacious effects with timely administration and monitoring of adverse events. Large-scale prospective randomized studies are required to assess the role of antiviral drugs for the treatment of this high mortality infection.

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[Available online at this link](https://www.knowledgeshare.nhs.uk/index.php?PageID=link_resolver&link=f64b801da4ac80745c9814fbd792985c)

1. **Increased urinary angiotensin converting enzyme 2 and neprilysin in patients with type 2 diabetes.**  
   Gutta Sridevi American journal of physiology. Renal physiology 2018;315(2):F263.

Angiotensin converting enzyme 2 (ACE2) and neprilysin (NEP) are metalloproteases that are highly expressed in the renal proximal tubules. ACE2 and NEP generate renoprotective angiotensin (1-7) from angiotensin II and angiotensin I, respectively, and therefore could have a major role in chronic kidney disease (CKD). Recent data demonstrated increased urinary ACE2 in patients with diabetes with CKD and kidney transplants. We tested the hypothesis that urinary ACE2, NEP, and a disintegrin and metalloproteinase 17 (ADAM17) are increased and could be risk predictors of CKD in patients with diabetes. ACE2, NEP, and ADAM17 were investigated in 20 nondiabetics (ND) and 40 patients with diabetes with normoalbuminuria (Dnormo), microalbuminuria (Dmicro), and macroalbuminuria (Dmacro) using ELISA, Western blot, and fluorogenic and mass spectrometric-based enzyme assays. Logistic regression model was applied to predict the risk prediction. Receiver operating characteristic curves were drawn, and prediction accuracies were calculated to explore the effectiveness of ACE2 and NEP in predicting diabetes and CKD. Results demonstrated that there is no evidence of urinary ACE2 and ADAM17 in ND subjects, but both enzymes were increased in patients with diabetes, including Dnormo. Although there was no detectable plasma ACE2 activity, there was evidence of urinary and plasma NEP in all the subjects, and urinary NEP was significantly increased in Dmicro patients. NEP and ACE2 showed significant correlations with metabolic and renal characteristics. In summary, urinary ACE2, NEP, and ADAM17 are increased in patients with diabetes and could be used as early biomarkers to predict the incidence or progression of CKD at early stages among individuals with type 2 diabetes.

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[Available online at this link](https://www.knowledgeshare.nhs.uk/index.php?PageID=link_resolver&link=8191c3936bf3f44512ec6811cf3dc4f8)

1. **Prevalence of comorbidities in the Middle East respiratory syndrome coronavirus (MERS-CoV): a systematic review and meta-analysis.**  
   Badawi Alaa International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases 2016;49:129-133.

The Middle East respiratory syndrome coronavirus (MERS-CoV) is associated with life-threatening severe illnesses and a mortality rate of approximately 35%, particularly in patients with underlying comorbidities. A systematic analysis of 637 MERS-CoV cases suggests that diabetes and hypertension are equally prevalent in approximately 50% of the patients. Cardiac diseases are present in 30% and obesity in 16% of the cases. These conditions down-regulate the synthesis of proinflammatory cytokines and impair the host's innate and humoral immune systems. In conclusion, protection against MERS-CoV and other respiratory infections can be improved if public health vaccination strategies are tailored to target persons with chronic disorders.

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1. **Inhibition of endoplasmic reticulum-resident glucosidases impairs severe acute respiratory syndrome coronavirus and human coronavirus NL63 spike protein-mediated entry by altering the glycan processing of angiotensin I-converting enzyme 2.**  
   Zhao X. Antimicrobial agents and chemotherapy 2015;59(1):206-16.

Endoplasmic reticulum (ER)-resident glucosidases I and II sequentially trim the three terminal glucose moieties on the N-linked glycans attached to nascent glycoproteins. These reactions are the first steps of N-linked glycan processing and are essential for proper folding and function of many glycoproteins. Because most of the viral envelope glycoproteins contain N-linked glycans, inhibition of ER glucosidases with derivatives of 1-deoxynojirimycin, i.e., iminosugars, efficiently disrupts the morphogenesis of a broad spectrum of enveloped viruses. However, like viral envelope proteins, the cellular receptors of many viruses are also glycoproteins. It is therefore possible that inhibition of ER glucosidases not only compromises virion production but also disrupts expression and function of viral receptors and thus inhibits virus entry into host cells. Indeed, we demonstrate here that iminosugar treatment altered the N-linked glycan structure of angiotensin I-converting enzyme 2 (ACE2), which did not affect its expression on the cell surface or its binding of the severe acute respiratory syndrome coronavirus (SARS-CoV) spike glycoprotein. However, alteration of N-linked glycans of ACE2 impaired its ability to support the transduction of SARS-CoV and human coronavirus NL63 (HCoV-NL63) spike glycoprotein-pseudotyped lentiviral particles by disruption of the viral envelope protein-triggered membrane fusion. Hence, in addition to reducing the production of infectious virions, inhibition of ER glucosidases also impairs the entry of selected viruses via a post-receptor-binding mechanism.

1. **Urinary angiotensin converting enzyme 2 increases in patients with type 2 diabetic mellitus.**  
   Liang Yaoxian Kidney & blood pressure research 2015;40(2):101-110.

BACKGROUND/AIMSAngiotensin converting enzyme 2 (ACE2) is highly expressed in the kidney and recognized to be renoprotective by degrading Angiotensin II to Angiotensin (1-7) in diabetic nephropathy. However, little is known about the role of urinary ACE2 (UACE2) in diabetes. The present study was performed to evaluate UACE2 levels in type 2 diabetic patients with various degrees of albuminuria and its associations with metabolic parameters. The effect of RAS inhibitors on UACE2 excretion was also assessed.METHODSA total of 132 type 2 diabetic patients with different degrees of albuminuria and 34 healthy volunteers were studied. UACE2 levels and activity were measured.RESULTSCompared to healthy controls, UACE2 to creatinine (UACE2/Cr) levels were significantly increased in both albuminuric and non-albuminuric diabetic patients. UACE2/Cr levels were much higher in hypertensive diabetic patients compared with their normotensive counterparts and treatment with RAS inhibitors markedly attenuated the augmentation. Furthermore, UACE2/Cr was positively correlated with fasting blood glucose, hemoglobin A1C (HbA1C), triglyceride, and total cholesterol. In multiple regression analysis, UACE2/Cr was independently predicted by HbA1C and RAS inhibitors treatment.CONCLUSIONSUACE2 increased in type 2 diabetic patients with various degrees of albuminuria and RAS inhibitors suppresses UACE2 excretion. UACE2 might potentially function as a marker for monitoring the metabolic status and therapeutic response of RAS inhibitors in diabetes.

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1. **Urinary angiotensin-converting enzyme 2 in hypertensive patients may be increased by olmesartan, an angiotensin II receptor blocker.**  
   Furuhashi Masato American journal of hypertension 2015;28(1):15-21.

BACKGROUNDAngiotensin-converting enzyme 2 (ACE2) is highly expressed in the kidney and converts angiotensin (Ang) II to Ang-(1-7), a renoprotective peptide. Urinary ACE2 has been shown to be elevated in patients with chronic kidney disease. However, the effects of antihypertensive agents on urinary ACE2 remain unclear.METHODSOf participants in the Tanno-Sobetsu cohort study in 2011 (n = 617), subjects on no medication (n = 101) and hypertensive patients treated with antihypertensive agents, including the calcium channel blockers amlodipine and long-acting nifedipine; the ACE inhibitor enalapril; and the Ang II receptor blockers losartan, candesartan, valsartan, telmisartan, and olmesartan, for more than 1 year (n = 100) were enrolled, and urinary ACE2 level was measured.RESULTSGlucose and hemoglobin A1c were significantly higher in patients treated with enalapril, telmisartan or olmesartan than in the control subjects. Urinary albumin-to-creatinine ratio (UACR) was significantly higher in patients treated with enalapril than in the control subjects. Urinary ACE2 level was higher in the olmesartan-treated group, but not the other treatment groups, than in the control group. Urinary ACE2 level was positively correlated with systolic blood pressure (r = 0.211; P = 0.003), UACR (r = 0.367; P < 0.001), and estimated salt intake (r = 0.260; P < 0.001). Multivariable regression analysis after adjustment of age, sex, and the correlated indices showed that the use of olmesartan was an independent predictor of urinary ACE2 level.CONCLUSIONSIn contrast with other antihypertensive drugs, olmesartan may uniquely increase urinary ACE2 level, which could potentially offer additional renoprotective effects.

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1. **Urinary angiotensin-converting enzyme 2 increases in diabetic nephropathy by angiotensin II type 1 receptor blocker olmesartan.**  
   Abe Masanori Journal of the renin-angiotensin-aldosterone system : JRAAS 2015;16(1):159-164.

INTRODUCTIONAngiotensin-converting enzyme 2 (ACE2) is a member of the renin-angiotensin system that degrades angiotensin (Ang) II to the seven-amino acid peptide fragment Ang-(1-7). We evaluated the changes in urinary ACE2 levels in response to treatment with the angiotensin II type 1 receptor blocker olmesartan in diabetes patients with nephropathy.MATERIALS AND METHODSThis prospective, open-label, interventional study was conducted with 31 type 2 diabetes patients with nephropathy. After initial evaluation, patients received 20 mg/day olmesartan, which was increased to 40 mg/day over a 24-week period.RESULTSIn diabetes patients with chronic kidney disease, olmesartan significantly increased urinary ACE2 levels independently of blood pressure and plasma aldosterone levels and reduced albuminuria, urinary liver-type fatty acid binding protein (L-FABP), and plasma aldosterone levels. Multivariable regression analysis revealed that the change in urinary L-FABP levels was an independent predictor of increased urinary ACE2 levels.CONCLUSIONOlmesartan may have the unique effect of increasing urinary ACE2 levels. However, whether this contributes to olmesartan's renoprotective effect must be examined further.

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1. **Angiotensin converting enzyme 2: a new important player in the regulation of glycemia.**  
   Chhabra Kavaljit H. IUBMB life 2013;65(9):731-738.

In spite of the novel antidiabetic drugs available on the market, type 2 diabetes mellitus (T2DM) affects nearly 25 million people in the USA and causes about 5% of all deaths globally each year. Given the rate and proportion by which T2DM is affecting human beings, it is indispensable to identify new therapeutic targets that can control the disease. Recent preclinical and clinical studies suggest that attenuating the activity of the renin-angiotensin system (RAS) could improve glycemia in diabetic patients. Angiotensin-converting enzyme 2 (ACE2) counteracts RAS overactivity by degrading angiotensin-II (Ang-II), a vasoconstrictor, to Ang-(1-7) which is a vasodilator. A decrease in ACE2 and an increase in A disintegrin and metalloproteinase (ADAM17)-mediated shedding activity have been observed with the progression of T2DM, suggesting the importance of this mechanism in the disease. Indeed, restoration of ACE2 improves glycemia in db/db and Ang-II-infused mice. The beneficial effects of ACE2 can be attributed to reduced oxidative stress and ADAM17 expression in the islets of Langerhans in addition to the improvement of blood flow to the β-cells. The advantage of ACE2 over other RAS blockers is that ACE2 not only counteracts the negative effects of Ang-II but also increases Ang-(1-7)/Mas receptor (MasR) [a receptor through which Ang-(1-7) produces its actions] signaling in the cells. Increased Ang-(1-7)/MasR signaling has been reported to improve insulin sensitivity and glycemia in diabetic animals. Altogether, ACE2/Ang-(1-7)/MasR axis of the RAS appears to be protective in T2DM and strategies to restore ACE2 levels in the disease seem to be a promising therapy for Ang-II-mediated T2DM.

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1. **Increased urinary angiotensin-converting enzyme 2 in renal transplant patients with diabetes.**  
   Xiao Fengxia PloS one 2012;7(5):e37649.

Angiotensin-converting enzyme 2 (ACE2) is expressed in the kidney and may be a renoprotective enzyme, since it converts angiotensin (Ang) II to Ang-(1-7). ACE2 has been detected in urine from patients with chronic kidney disease. We measured urinary ACE2 activity and protein levels in renal transplant patients (age 54 yrs, 65% male, 38% diabetes, n = 100) and healthy controls (age 45 yrs, 26% male, n = 50), and determined factors associated with elevated urinary ACE2 in the patients. Urine from transplant subjects was also assayed for ACE mRNA and protein. No subjects were taking inhibitors of the renin-angiotensin system. Urinary ACE2 levels were significantly higher in transplant patients compared to controls (p = 0.003 for ACE2 activity, and p≤0.001 for ACE2 protein by ELISA or western analysis). Transplant patients with diabetes mellitus had significantly increased urinary ACE2 activity and protein levels compared to non-diabetics (p<0.001), while ACE2 mRNA levels did not differ. Urinary ACE activity and protein were significantly increased in diabetic transplant subjects, while ACE mRNA levels did not differ from non-diabetic subjects. After adjusting for confounding variables, diabetes was significantly associated with urinary ACE2 activity (p = 0.003) and protein levels (p<0.001), while female gender was associated with urinary mRNA levels for both ACE2 and ACE. These data indicate that urinary ACE2 is increased in renal transplant recipients with diabetes, possibly due to increased shedding from tubular cells. Urinary ACE2 could be a marker of renal renin-angiotensin system activation in these patients.

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1. **ACE2, a promising therapeutic target for pulmonary hypertension.**  
   Shenoy Vinayak Current opinion in pharmacology 2011;11(2):150-155.

Pulmonary arterial hypertension (PAH) is a chronic lung disease with poor diagnosis and limited therapeutic options. The currently available therapies are ineffective in improving the quality of life and reducing mortality rates. There exists a clear unmet medical need to treat this disease, which necessitates the discovery of novel therapeutic targets/agents for safe and successful therapy. An altered renin-angiotensin system (RAS) has been implicated as a causative factor in the pathogenesis of PAH. Angiotensin II (Ang II), a key effector peptide of the RAS, can exert deleterious effects on the pulmonary vasculature resulting in vasoconstriction, proliferation, and inflammation, all of which contribute to PAH development. Recently, a new member of the RAS, angiotensin converting enzyme 2 (ACE2), was discovered. This enzyme functions as a negative regulator of the angiotensin system by metabolizing Ang II to a putative protective peptide, angiotensin-(1-7). ACE2 is abundantly expressed in the lung tissue and emerging evidence suggests a beneficial role for this enzyme against lung diseases. In this review, we focus on ACE2 in relation to pulmonary hypertension and provide proof of principle for its therapeutic role in PAH.

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1. **Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes.**  
   Yang Jin-Kui Acta diabetologica 2010;47(3):193-199.

Multiple organ damage in severe acute respiratory syndrome (SARS) patients is common; however, the pathogenesis remains controversial. This study was to determine whether the damage was correlated with expression of the SARS coronavirus receptor, angiotensin converting enzyme 2 (ACE2), in different organs, especially in the endocrine tissues of the pancreas, and to elucidate the pathogenesis of glucose intolerance in SARS patients. The effect of clinical variables on survival was estimated in 135 SARS patients who died, 385 hospitalized SARS patients who survived, and 19 patients with non-SARS pneumonia. A total of 39 SARS patients who had no previous diabetes and received no steroid treatment were compared to 39 matched healthy siblings during a 3-year follow-up period. The pattern of SARS coronavirus receptor-ACE2 proteins in different human organs was also studied. Significant elevations in oxygen saturation, serum creatinine, lactate dehydrogenase, creatine kinase MB isoenzyme, and fasting plasma glucose (FPG), but not in alanine transaminase were predictors for death. Abundant ACE2 immunostaining was found in lung, kidney, heart, and islets of pancreas, but not in hepatocytes. Twenty of the 39 followed-up patients were diabetic during hospitalization. After 3 years, only two of these patients had diabetes. Compared with their non-SARS siblings, these patients exhibited no significant differences in FPG, postprandial glucose (PPG), and insulin levels. The organ involvements of SARS correlated with organ expression of ACE2. The localization of ACE2 expression in the endocrine part of the pancreas suggests that SARS coronavirus enters islets using ACE2 as its receptor and damages islets causing acute diabetes.

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1. **Pharmacologic modulation of ACE2 expression.**  
   Soler María José Current hypertension reports 2008;10(5):410-414.

Angiotensin-converting enzyme 2 (ACE2) is an enzymatically active homologue of angiotensin-converting enzyme that degrades angiotensin I, angiotensin II, and other peptides. Recent studies have shown that under pathologic conditions, ACE2 expression in the kidney is altered. In this review, we briefly summarize recent studies dealing with pharmacologic interventions that modulate ACE2 expression. ACE2 amplification may have a potential therapeutic role for kidney disease and hypertension.

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1. **A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury**  
   Kuba Nature Medicine 2005;11(8):875-9.

During several months of 2003, a newly identified illness termed severe acute respiratory syndrome (SARS) spread rapidly through the world. A new coronavirus (SARS-CoV) was identified as the SARS pathogen, which triggered severe pneumonia and acute, often lethal, lung failure. Moreover, among infected individuals influenza such as the Spanish flu and the emergence of new respiratory disease viruses have caused high lethality resulting from acute lung failure. In cell lines, angiotensin-converting enzyme 2 (ACE2) has been identified as a potential SARS-CoV receptor. The high lethality of SARS-CoV infections, its enormous economic and social impact, fears of renewed outbreaks as well as the potential misuse of such viruses as biologic weapons make it paramount to understand the pathogenesis of SARS-CoV. Here we provide the first genetic proof that ACE2 is a crucial SARS-CoV receptor in vivo. SARS-CoV infections and the Spike protein of the SARS-CoV reduce ACE2 expression. Notably, injection of SARS-CoV Spike into mice worsens acute lung failure in vivo that can be attenuated by blocking the renin-angiotensin pathway. These results provide a molecular explanation why SARS-CoV infections cause severe and often lethal lung failure and suggest a rational therapy for SARS and possibly other respiratory disease viruses.

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