

Special Report from the Editor-in-Chief:

Cracking the code to the 2019 novel coronavirus (COVID-19): Lessons from the eye

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Abstract

With the recent March 11, 2020 declaration of a pandemic by the World Health Organization (WHO), further attention has turned to understanding and managing the outbreak of infectious disease termed coronavirus disease 2019 (COVID-19) caused by the novel coronavirus identified as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The SARS-CoV-2 gains entry into human cells through its ability to bind to a human ACE2 protein. Through our understanding of diabetic retinopathy, there are genetic-based variations in ACE2 levels that confer varying risk profiles for diabetic retinopathy. Similarly, emerging research suggests ACE2 levels confer varying risk profiles for COVID-19. Using data comparisons between geographic prevalence rates of diabetic retinopathy and existing COVID-19 mortality rates may enable improved predictions of the rates of spread of COVID-19 in various geographic regions. The goal of this report is to encourage cross-disciplinary horizontal vision in the

field of medicine and science in order to further progress in managing and treating human disease.

Geographic and Ethnic Variations in the Prevalence of Diabetic Retinopathy

Diabetic retinopathy is a form of diabetic eye disease in which damage from diabetes, particularly damage to the small retinal vessels, a process known as diabetic microvascular disease, progresses in concert with molecular disruption and dysfunction resulting in vision-threatening retinal damage. While the early stages of diabetic retinopathy may be asymptomatic, diabetic retinopathy is the leading causes of blindness among adults age 25 to 74 in the United States and the industrialized world.¹

It has been well-documented in the field of retina that there are ethnic and geographic variations in the prevalence of diabetic retinopathy in individuals who have type 2 diabetes. While the global prevalence of diabetic retinopathy in individuals with type 2

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diabetes is estimated to be approximately 25%, it varies by population, from lower percentages such as 22% in Italy and 23% in China to higher percentages such as 30% in the United Kingdom and 40% in the United States.² The pattern of this data has been replicated in multiple studies, and although there may be variations in geographic comparisons based on study dates and methodologies, there are many variables that affect the geographic differences in prevalence of diabetic retinopathy.^{3,4} These variables include, among others, socioeconomic factors such as access to health care, societal views on health care, the overall health of the population, nutritional differences, and environmental factors. An equally important set of variables are genetic variations and genetic susceptibilities.

ACE2 and Diabetic Retinopathy

One of these genetic variations may be in the gene for angiotensin-converting enzyme 2 (ACE2), a homologue of the enzyme angiotensin-converting enzyme (ACE) which controls blood pressure and blood flow through the renin-angiotensin system. The presence of ACE2 was first identified in the retina in 2004 and the activity of ACE2 was found to be increased in the retina in diabetes.^{5,6} More recently, there is a growing body of evidence that higher levels of ACE2 protect the retina from diabetic retinopathy, via vasodilation, neuroprotection, anti-inflammation, and anti-vascular proliferation mechanisms.⁷⁻¹³ Multiple studies have shown that genetically increasing levels of ACE2 (via gene therapy) results in decreased diabetic retinopathy⁷⁻¹⁰ and loss of genetic expression of ACE2 results in exacerbation of diabetic retinopathy.¹¹

Genetic-Based Variations in ACE2 Levels

ACE2 polymorphisms have been reported to be associated with varying risk profiles for diabetic retinopathy; specifically, in a Chinese population, these variations in ACE2 genes can confer risk of or protection from progression of diabetic retinopathy.¹⁴

Furthermore, in a large genetic study evaluating the heritable factors in hypertension, researchers found that up to 67% of the variability in levels of ACE2 circulating within an individual's bloodstream is controlled by one's genetics.¹⁵ In other words, the researchers identified that genetic variations, from one family pedigree to another, regulate ACE2 expression. Family origin and ethnicity play large roles in genetic variations, in general, and specifically polymorphisms in the ACE2 have been reported by ethnicity.¹⁶ Multiple reports have demonstrated that these polymorphism in ACE2 are associated with conferring risk of or protection from disease, such as hypertension.¹⁷ While the causal factors for diabetic retinopathy are certainly multifactorial, genetic variations in ACE2 and ACE2 expression profiles may play a partial role, perhaps even larger than expected, in explaining a portion of the geographic and ethnic variation in diabetic retinopathy.

ACE2 and Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)

The SARS-CoV-2, a positive-sense single strand RNA virus of the beta-subgroup of coronaviruses, is the causative agent of outbreak of infectious disease termed coronavirus disease 2019 (COVID-19). The SARS-CoV-2 is 79% homologues with its predecessor, the 2002 severe acute respiratory coronavirus (SARS-CoV). The SARS-CoV-2 uses the same ACE2 protein described above in order to gain entry into human cells; it needs this entry into the cell so that it can use the host human cell's apparatus to replicate itself.¹⁸ This ACE2 protein is located in multiple tissues other than the retina: the brain, heart, blood vessels, kidneys, gastrointestinal tract, and, to a lesser extent, the lungs.^{16,19} Within the lungs, the ACE2 protein is expressed more abundantly on the apical surface of lung alveolar epithelial cells.²⁰

Coronavirus are named after their crown-like appearance of spikes on their surface. The SARS-CoV spike protein binds to the ACE2 protein on the

surface of the lung cells to mediate entry of the virus RNA into the cell.²¹ Specifically, the receptor-binding domain of the spike protein mediates this virus-to-cell interaction, effectively making the ACE2 protein the receptor for the virus.²² Furthermore, the affinity of the SARS-CoV spike protein to the ACE2 protein is crucial in mediating infection.²³ In *Ace2* knockout mice (missing the expression of ACE2), infectious SARS-CoV levels were very low, confirming the need for expression of ACE2 in humans for SARS-CoV infection.²⁴

There are genetic variations in ACE2 which may result in different expression levels or patterns, or even binding affinity of the SARS-CoV to the human ACE2 protein.^{25,26} Specifically, researchers have identified that these genetic variations correlate with geographic populations and ethnicities: “East Asian populations have ... higher ACE2 expression in tissues”.²⁵ As there is emerging research on COVID-19, recent additional non-peer reviewed (preprint) data confirms the higher ACE2 expression in Asian populations²⁷ as well as in other specific non-ethnic demographics, such as tobacco-use.²⁸

Geographic Comparison of Prevalence of Diabetic Retinopathy with COVID-19 Mortality

As identified above, the genetic variations in ACE2 expression confer varying risk of diabetic retinopathy and of COVID-19. Specifically, increased ACE2 expression may confer a degree of protection against diabetic retinopathy but may confer a degree of increased risk against COVID-19. Using data from the WHO,²⁹ as of March 14, 2020, there is a degree of correlation between geographic areas of low diabetic retinopathy and areas of high COVID-19 mortality (Figure 1). Standard linear regression analysis using the slope formula demonstrates decreased COVID-19 mortality with increased prevalence of diabetic retinopathy.

Conclusions

While the data presented in Figure 1 is certain to be constrained and flawed to an extent, as (1) there are likely regional differences in methods of identifying infected patients as well as in the reporting of these patients, (2) the data collected (although all on the same date of March 14, 2020) is from differing timepoints from when the outbreak started in each region, and (3) the underlying etiologies of health conditions such as diabetic retinopathy and COVID-19 are all multifactorial, it is this type of data that must be used to generate scientific hypotheses to test in order to identify effective treatment strategies in a timely manner.

The data available to date suggest that further evaluation of ACE2 expression is critical to understanding targeted therapeutic strategies for COVID-19. Furthermore, this knowledge is essential as it may be used to predict the progress and path of COVID-19. While there is much speculation that people with asymptomatic infections may be driving the spread of COVID-19, it may be even more critical in geographic regions such as the United States where, if the theory presented in Figure 1 is correct, then there may be lower disease severity and higher rates of asymptomatic infected people. In this case, the exponential rate of expansion of COVID-19 cases would be even greater than expected (though the end of the outbreak perhaps may be sooner than expected). In events which grow exponentially such as the spread of COVID-19, the time to act to prevent excess mortality is now (or yesterday in the calm before the storm), particularly if the exponential rate of spread is greater than expected.

Cross-disciplinary vision is often essential to cracking the code in a variety of diseases. In an era of high degrees of scientific specialization, the so-often hyper-specialization leads to a discontinuity in the ability to view the entirety of the issues involved. The network then required to achieve the goal is fragmented. Integration of various disciplines is often

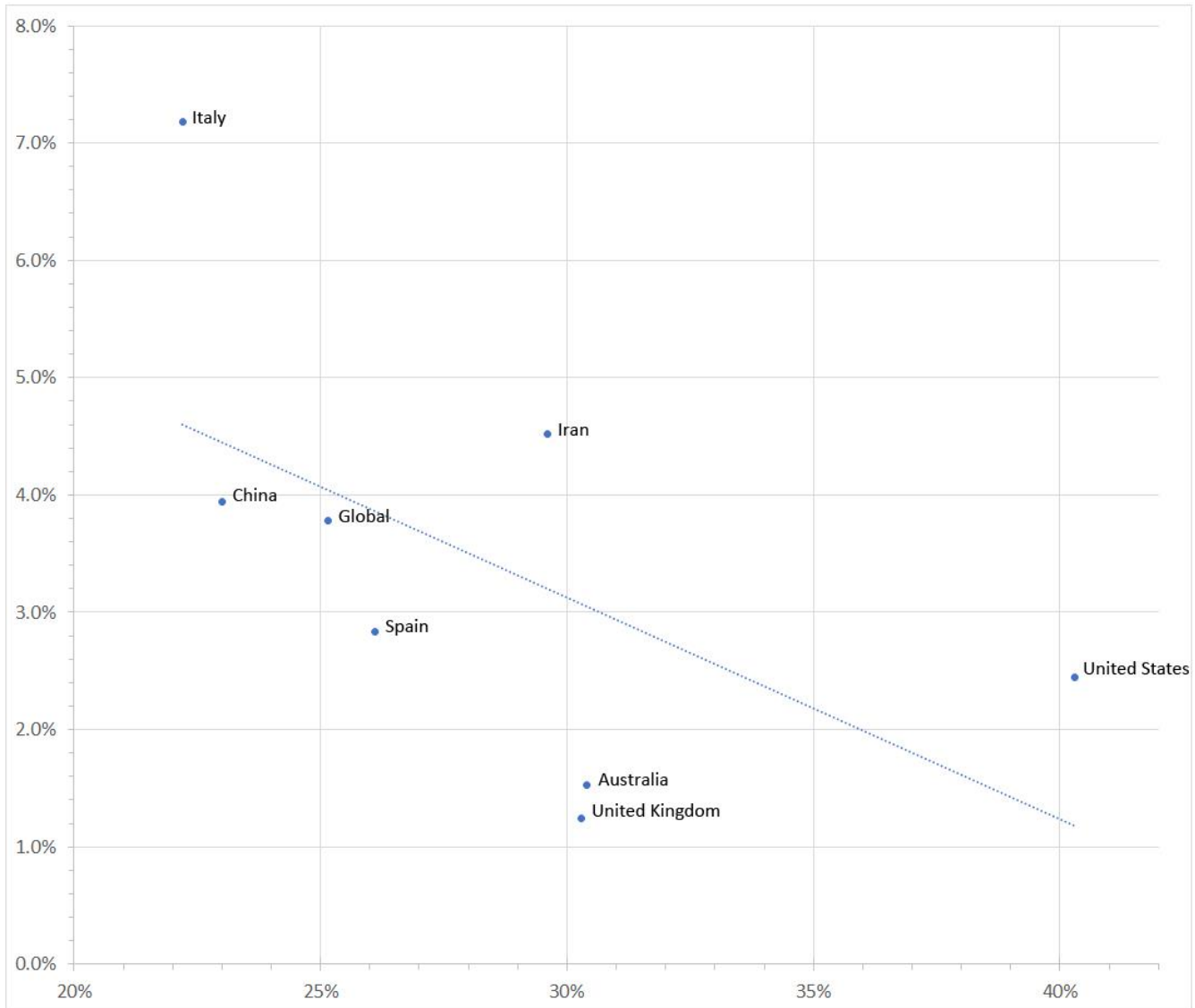


Figure 1

COVID-19 Mortality as a Function of Diabetic Retinopathy Prevalence in Select Countries. The prevalence rate of diabetic retinopathy (x-axis) in patients with type 2 diabetes in select countries in whom the prevalence is well-identified is compared with the mortality rate of COVID-19 (y-axis) as of March 14, 2020 in select countries in whom the infection rate and mortality rate are both sufficiently high such that the rate is well-identified. These select countries are as follows, with

diabetic retinopathy rates followed by COVID-19 mortality rates in parentheses: Italy (22.2%, 7.2%), China (23.0%, 3.9%), Spain (26.1%, 2.8%), Iran (29.6%, 4.5%), the United Kingdom (30.3%, 1.3%), Australia (30.4%, 1.5%), and the United States (40.3%, 2.4%). The global rate of diabetic retinopathy is 25.2% and of COVID-19 mortality is 3.8%. The linear regression line of best fit is shown in blue, demonstrating decreased COVID-19 mortality with increased prevalence of diabetic retinopathy.

required to understand the full breadth of the challenges at hand. Perspectives must be broadened with “horizontal vision” to see the complex and interconnected portions of scientific knowledge. As John Barry writes in *The Great Influenza: The Story of the Deadliest Pandemic in History*, examining the 1918 flu pandemic:

The greatest challenge of science, its art, lies in asking an important question and framing it in a way that allows it to be broken into manageable pieces, into experiments that can be conducted that ultimately lead to answers. To do this requires a certain kind of genius, one that probes vertically and sees horizontally.

Horizontal vision allows someone to assimilate and weave together seemingly unconnected bits of information. It allows an investigator to see what others do not see, and to make leaps of connectivity and creativity. Probing vertically, going deeper and deeper into something, creating new information. Sometimes what one finds will shine brightly enough to illuminate the whole work.

... To see questions in these ways requires a wonder, a deep wonder focused by discipline, like a lens focusing the sun’s rays on a spot of paper until it bursts into flame. It requires a kind of conjury.³⁰

There is much more knowledge needed regarding ACE2, whether in its relation to COVID-19, diabetic retinopathy, or other human disease. The goal of this report is to encourage this type of horizontal vision that all of us in the field of medicine and science must seek to achieve in order to further progress in managing and treating human disease.

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