



Wherever the art of medicine is loved, there is also a love of humanity. - Hippocrates

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Editorial

COVID-19: Public Policy and Impact on Healthcare

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Over the past 6 months, COVID-19 has killed hundreds of thousands of people truly testing healthcare system capacities to manage critically ill patients around the world. In the United States alone this coronavirus pandemic has exposed our healthcare system's weaknesses and lack of preparedness. Scenes of overwhelmed emergency departments in the worst affected areas helped spur a public crisis response that included both widespread shelter-in-place orders and unprecedented

government expenditures. Despite these efforts, there were still several areas that struggled with inadequate critical care beds, personal protective equipment and mechanical ventilators. Today the pandemic rages on, with the United States reporting the highest number of cases and deaths globally. It is imperative that we examine more closely the steps we have taken thus far, and what we have yet to accomplish and think about it in a broader sense of public health.

Legislative Initiatives: The Coronavirus Aid Relief, and Economic Security (CARES) Act was a \$2.2 trillion relief bill signed by President Trump on March 27, 2020 (1). The goal of the bill was to provide economic support to American workers, small businesses and state and local governments (2). However, funding under the CARES Act quickly depleted and the \$484 billion Paycheck Protection Program and Health Care Enhancement Act (COVID-3.5) was signed into law on April 24th as an extension of the former Act (3).

Key Features of CARES Act

- Expansion of telehealth opportunities
- Medicare advance payments for emergency visits
- Financial assistance for student loans/deferral of payments
- Reimbursement for healthcare providers for lost revenue or expenses related to COVID- 19
- Liability limitations and coverage of COVID testing and preventive services

The Health and Economic Recovery Omnibus Emergency Solutions (HEROES) Act was passed by the U.S. House on May 15, 2020. This legislation plans to provide more than \$1 trillion to state governments for expenditures including expanded unemployment benefits, hazard pay for frontline workers, student loan forgiveness, increased food stamp funding and direct cash payments for up to \$6,000 per family (4). The senate has not yet approved this bill.

Regulatory Initiatives: Under Section 1135 of the Social Security Act, the Centers of Medicare and Medicaid Services (CMS) may temporarily waive or modify certain Medicare and Medicaid requirements (5). The Emergency Medical Treatment and Labor Act (EMTALA) is a federal law passed in 1986 that requires anyone coming to an Emergency Department (ED) to be stabilized and treated, regardless of their insurance status or ability to pay (6). CMS clarified that EMTALA requirements DO NOT apply to drive through testing sites for COVID-19, including those located on a hospital campus. Additionally, triage nurses may redirect patients coming into the Emergency Medicine Departments (ED) to another area for a medical screening exam to cohort those with respiratory symptoms. As an Emergency Room doctor, I saw this firsthand in effect, where patients with COVID-like symptoms were screened via telehealth and cohorted in areas outside the ED to prevent the spread of the infection within the hospital.

CMS also issued a number of waivers to encourage greater use of telehealth services. Key changes included geographic expansion of telehealth to include patients living in urban areas and waived HIPAA requirements to allow use of modalities such as Facetime and Skype to further increase accessibility. We did this in our Level 1 Trauma Hospital in an urban area. We used telehealth to evaluate and treat ill, but stable COVID-19 patients and discharged them from outside the ED. This was a form of healthcare practice I was never trained under EMTALA.

Other waivers include expansion of the telehealth service list to include additional billing codes for the ED evaluation and waiving patient cost sharing such as deductibles, coinsurance and copayments. Lastly there is a temporary waiver to allow physicians who are licensed in one state to provide telehealth services to a patient in another state although this generally is still subject to the jurisdiction of states to address.

Future of COVID-19 Policy: Perhaps the most pressing COVID-related policy question is when and at what pace states or localities should re-open their economies. Unfortunately, this debate has become increasingly partisan. Political leaders face the dual challenges of balancing the healthcare risks related to a lethal pandemic versus what may become one of the worst economic depressions in history. These are usually framed as trade off: *save jobs or save lives*. But it is not all clear that this is the case: premature lifting of public health measures followed by a COVID-19 resurgence may cause more long-term economic damage than a slower more methodical approach that initially keeps business shuttered longer.

The overarching goal of expert guidance on reopening is to drive R0 below one. R0 is the reproductive number of the virus: it refers to the number of people on average that one person with COVID-19 will infect. If R0 is above one, each new generation of infected people will be larger than the last and the outbreak will spiral out of control. If the R0is less than one, each generation of infected people will be smaller than the last and the outbreak will eventually die out.

Criteria for Safe Reopening

- Sustained reduction in cases for 14 days
- Hospitals can treat all patients requiring hospitalization without resorting to crisis standards
- The state is able to test all people with COVID-19 symptoms
- The state is able to conduct active monitoring of confirmed cases and their contacts

Another unsettled issue involves healthcare coverage for the uninsured Americans infected by COVID. Even if the federal government will pick up this tab, many questions remain, including whether services such as post-hospital care for critically ill survivors will be available and how they will be covered. On average an intubated survivor of COVID-19 in March needed strict pulmonary rehab, physical therapy, psychiatric care and much more until past August, and is continuing.

Finally, this unprecedented period of our history will likely end only with the successful development, manufacture, distribution, and administration of a novel coronavirus vaccine. We will not be able to make vaccines available immediately to every person, and the timeline for the vaccine release remains unclear. However, some prioritization system for administration of vaccines will have to occur, and future debate regarding the topic of vaccination is certain and undoubtedly necessary. This discussion will continue.

Disclosure: The author declared no competing interests.

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- 3. H.R. 266: Paycheck Protection Program and Health Care Enhancement Act. https://www.govtrack.us/congress/bills/116/hr266
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- 5. Section 1135 of Social Security Act: Authority to waive requirements during national emergencies https://www.ssa.gov/OP Home/ssact/title11/1135.htm
- Emergency Medical Treatment and Labor Act (EMTALA) <u>https://www.cms.gov/Regulations-and-Guidance/Legislation/EMTALA</u>

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A Piece of My Mind Virtual Clinical Trials: Has the COVID-19 Pandemic Served as a Catalyst in Accelerating These?

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Virtual Clinical Trials (VCT): Clinical trials are the basis of innovation. They form the basis of improving patient care-from drug development, controlled use in patients and observation of efficacy end point, monitoring safety data and ultimately bringing the drug from the bench to bed side i.e. for use in patients The huge hurdles in this pathway are the lengthy time process, expenses involved, inability to enroll large number of patients, cross geographic barriers, missing real world clinical practice and lacking disease heterogeneity. VCT could be a potential solution to these problems. Leveraging the digital technology i.e. mobile devices, mobile apps, remote monitoring devices, and online social engagement platforms VCT can provide solutions to a few of the hurdles that traditional clinical trials in the brick and mortar setting face.

The COVID-19 pandemic ushered us all, healthcare providers and healthcare systems to adopt and embrace telemedicine like it was never before. The Centers for Medicare and Medicaid Services (CMS) allowed reimbursement for the telemedicine services provided and other private payors followed suit as well. The silver lining, if any of the dark clouds of the pandemic could include, is VCT implementation for better patient care in an expedited way. Both the providers and patients are now familiar with the use of digital technology, its use in healthcare more than in the pre COVID-era.

Advantages: VCT provides a comprehensive package of opportunities to improve the clinical trials arena. It cuts down the operational costs by reducing the requirement for brick and mortar places, reduces the financial burden of travel of patients multiple times to the trial center locations, increases patient enrollment, engagement and retention. The collection of data being continuous and real time has its advantages of providing comprehensive information rather than being snapshot data. Incorporation of this real time data with existing electronic health records should not be a daunting task.

Challenges: The seemingly exciting proposal has its own challenges as expected. One size does not fit all the needs. Interventional studies could pose more challenges than observational studies. Maintaining patient privacy, ensuring the regulatory requirements are satisfied, and safety of patients on the top are not easy. In this learning curve the other potential challenges could be being compliant with different licensing requirements for telemedicine across the state borders, operational issues like supply chain of personnel, drug delivery, HIPAA compliance with the devices provided to patients, conforming to the privacy laws and informed consent among others.

Take Home Message: Stay tuned for exciting change in your clinical trials practice, and read the following articles, which are good sources of VCT that might be interesting.

Disclosure: Author declared no competing interests.

- Using Technologies and Innovative Methods To Conduct Food and Drug Administration-Regulated Clinical Investigations of Investigational Drugs; Establishment of a Public Docket. <u>https://www.federalregister.gov/documents/2015/10/29/2015-27581/using-technologies-and-innovative-methods-to-conduct-food-and-drug-administration-regulated-clinical</u>
- Trials Built for the Age of Innovation. https://www.iqvia.com/solutions/research-and-development/clinical-trials
- Virtual Clinical Trials: Testing New Drugs Afar, Harvard University, <u>http://sitn.hms.harvard.edu/flash/2019/virtual-clinical-trials-testing-new-drugs-afar/</u>
- Virtual Clinical Trials: Challenges and Opportunities: Proceedings of a Workshop, National Academies Press. <u>https://www.ncbi.nlm.nih.gov/books/NBK548981/</u>

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Gliflozins: Are They Wonder Drugs?

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Prologue: Ever since Banting and Best discovered insulin in 1960s, the treatment of type-2 diabetes mellitus (T2DM) was not only fascinating and challenging, but also frustrating. Despite the advent of several new classes of medicines, achieving a perfect glycemic control is easier said than done. Then came the gliflozins or the SGLT-2 inhibitors, which appeared like the Holy Grail of glycemic control. There was never such a great moment in the practice of an Internist or Family Medicine Physician to see even their non-compliant diabetic patients showing low HbA1c levels. Added to that, literature is riddled with several other benefits of gliflozins, such as loss of body weight, decrease in blood pressure and serum uric acid levels, which have been difficult to achieve in T2DM patients treated with other medications. Despite these and other documented advantages in using gliflozins, thus making them sound like Wonder Drugs, there have been several questions on the safety and other unwanted effects of gliflozins. While most of them are straight forward to answer, others seem to be complex to understand or address. Let us examine the advantages and disadvantages in using gliflozins in T2DM patients.

What are Gliflozins? Gliflozins are chemical compounds that inhibit sodium glucose-cotransporter-2 (SGLT-2) in the proximal tubules of the kidney (Mosely et al, 2015). All the glucose in plasma is filtered at the glomerulus and then reabsorbed almost completely in the proximal tubule through SGLT-2. Glucose appears in the urine only when this reabsorptive capacity of the proximal tubules is overwhelmed, i.e., high blood glucose levels. By inhibiting the SGLT-2 in the kidney, gliflozins decrease the blood glucose levels, independent of insulin. In this respect gliflozins are unique anti-diabetic drugs. Other anti-diabetic drugs decrease blood glucose levels by increasing glucose uptake into tissues and/or increasing glucose utilization by cells. Gliflozins simply get rid of glucose in the urine through the kidney. While it seems to be a simple and straightforward process, free from complications, in reality, it is not that simple and this process is associated with several other changes in the physiology and body's ability to adapt (see below). Phloretin, a natural compound was originally observed to cause renal loss of glucose, reversal of insulin resistance and normalization of plasma glucose levels in diabetic animals by non-selectively inhibiting both SGLT-1 and SGLT-2. Phloretin is not suitable for use as a drug due to its poor bioavailability when administered orally, and inhibition of SGLT-1 causes diarrhea and nausea. Hence, derivatives of phloretin that selectively inhibit SGLT-2 and are active when orally administered were made, which are called gliflozins. There are four types of gliflozins currently available for diabetic treatment, namely Canagliflozin, Dapagliflozin, Empagliflozin and Ertugliflozin. Another drug, Sotagliflozin, a dual SGLT-1/SGLT-2 inhibitor has been approved by the European Union for treatment of certain types of T1DM. However, the US Food and Drug Administration has declined the approval of Sotagliflozin for treatment of T1DM in combination with insulin (Habtemariam, 2019).

Advantages: Gliflozins offer several advantages over other anti-diabetic drugs. First, due to excellent oral bioavailability, and long elimination half-life they allow once-daily administration. They show durable clinical efficiency in controlling hyperglycemia when used as monotherapy or in combination with other anti-diabetic drugs, such as metformin or insulin or DPP-4 inhibitors, thus reducing HbA1c to target levels without increasing the number of major hypoglycemic episodes. Combination of gliflozins with metformin also reduces body weight steadily, which is comparable to the weight loss achieved by the administration of glitazones. The net effective glycemic control and weight loss translate into control of blood pressure, with decreases in both systolic and diastolic readings (reviewed in Hossain and Pervin, 2018). • Another beneficial effect of long-term use of gliflozins is reduction in serum uric acid levels. Although seen as another blood parameter, uric acid links kidney with diabetes and hypertension. An end-product of purine metabolism, uric acid levels in the blood are elevated in T2DM, often leading to gout. Uric acid in turn inhibits insulin signaling. Interestingly, insulin therapy also raises blood uric acid levels. Thiazide diuretics used to treat hypertension also cause elevation in blood uric acid levels. Elevated uric acid levels cause inflammation and increase blood pressure. Thus, it appears that uric acid is a culprit in both T2DM and

hypertension making it hard to treat these two conditions, Ironically, lowering blood uric acid levels with allopurinol in T2DM patients does not improve diabetic condition. In this context, gliflozins increase urinary excretion of uric acid and this prevents a rise in blood uric acid levels, which may also account for decreased blood pressure (reviewed in Kishore BK, 2019). • The Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes (EMPA-REG-OUTCOMES) trial studies funded by Boehringer Ingelheim and Eli Lilly, showed that in patients with T2DM at high risk for cardiovascular events who received Empagliflozin, as compared with placebo, had a lower rate of the primary composite cardiovascular outcome and of death from any cause when the study drug was added to standard care (Zinman et al, 2015). These clinical trials coupled with studies in diabetic *db/db* mouse models have led to the growing case for use of SGLT-2 inhibitors in heart failure (Ha and Wende, 2019). • Interestingly, in a non-diabetic rodent model of heart failure with preserved ejection fraction (HFpEF), Empagliflozin improved diastolic function, thus giving hope for the treatment of one of the exceptionally resistant cardiovascular conditions to current therapy options (Connelly et al, 2019). • Thus, the potential beneficial effects of gliflozins go far beyond effective glycemic control in T2DM. Recently the FDA approved the use of gliflozins for a number of conditions. Specifically, in 2018, Canagliflozin was approved to reduce the risk of major heart-related events such as heart attack, stroke, or death in patients with T2DM who have known heart disease; and, in 2019, it was approved to reduce the risk of end-stage kidney disease, worsening of kidney function, heart-related death, and being hospitalized for heart failure in certain patients with T2DM and diabetic kidney disease (US FDA Drug Safety, August 2020).



Schematic representation of the beneficial and adverse effects of SGLT-2 inhibitors on various physiological parameters. Reproduced with permission from <u>Jean-Luc Faillie, 2017</u>, Pharmacological Aspects of the Safety of Gliflozins. *Pharmacol Res* 118:71-81.

Disadvantages: Despite the above list of beneficial effects, gliflozins do have some unwanted and serious side effects. The common ones are modest polyuria, which is inconvenient and may cause volume depletion; urinary tract infections,

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especially among women. • FDA also warned of a rare occurrence of serious infections of genital area (US FDA Drug Safety, August 2018). • Although recently FDA has removed the Boxed Warning about increased risk of foot and leg amputations among the users of SGLT-2 inhibitors, it has not removed the basic warning. Hence, monitoring of the patients on longterm therapy with gliflozins is needed. • Gliflozins can also cause euglycemic diabetic ketoacidosis (DKA) due to decreased production of endogenous insulin and reduced need for exogenous insulin as well as enhanced fatty acid oxidation (Yokono et al, 2014), and also by apparent inhibition of renal tubular absorption of ketone bodies (Qiu et al, 2017). Ketone bodies are known to interfere with creatinine secretion in the kidney, and thus may spuriously impact urinary creatinine albumin ratio (UCAR) in patients with diabetic nephropathy (reviewed in Kishore BK, 2019). • A guideline from the Government of the United Kingdom directed that SGLT-2 inhibitor treatment should be interrupted in patients who are hospitalized for major surgical procedures or acute serious medical illnesses and ketone levels measured, preferably in blood rather than in urine. Treatment may be restarted when the ketone values are normal and the patient's condition has stabilized (GOV.UK Drug Safety Update, March 2020). • Furthermore, patients on a combination therapy of metformin and SGLT-2 inhibitors may develop life-threatening metabolic acidosis with high anion gap by a combination of metformin-induced lactic acidosis and SGLT-2 inhibitors-induced ketoacidosis (US FDA Drug Safety, May 2015; US FDA Drug Safety, March 2020). • Decreasing renal function (eGFR <60 mL/min/1.73m²) causes higher AUC (Area Under Curve) of gliflozins plasma levels, thus increases adverse effects. However, patients receiving dialysis have lesser or no increases in AUC. Despite the increase in AUC, the pharmacodynamic response to SGLT-2 inhibitors as assessed by urinary glucose excretion declines by increasing severity of renal functional impairment, as the kidneys can no longer promote glucose excretion into the urine. Interestingly, however, in T2DM patients with stage 3 chronic kidney disease, Dapagliflozin did not improve glycemic control but reduced body weight and blood pressure compared with placebo controls when used as an add-on therapy (reviewed in St. Peter et al, 2019). • The use of SGLT-2 inhibitors is also associated with bone demineralization and a potential risk for fractures. Recently, it has been documented that SGLT-2 inhibition indirectly triggers FGF23/1,25-dihydroxyvitamin D/parathyroid hormone axis, which may contribute to adverse effects on bone health (Blau et al, 2018). In a study of diabetic patients with moderate renal impairment, 9.4% of patients treated with Dapagliflozin (10 mg/day) experienced bone fractures, whereas no fractures were observed in placebo-treated patients (Kohan et al, 2013). • Although it was originally suspected based on limited short-term observations, currently available meta-analysis data from randomized clinical trials do not suggest a detrimental effect of SGLT-2 inhibitors on the incidence of malignancies in general, or in bladder cancer in particular (Dicembrini et al, 2019). •Finally, a recent review on potential benefits and harms of novel antidiabetic drugs during COVID-19 crisis cautioned: Metabolic decompensation toward DKA, either hyperglycemic or "euglycemic", in susceptible diabetic patients on SGLT2 inhibitors can be further exacerbated by volume depletion from persistent glycosuria. At initial symptoms of COVID-19 illness, patients with off-label prescription or long-lasting T2DM with severe β -cell insufficiency requiring insulin therapy should temporarily stop the SGLT2 inhibitor, contact their medical provider, monitor capillary blood ketones and take supplemental boluses of rapid insulin along with liquids and carbohydrates. A full episode of COVID-19-related DKA can be successfully prevented with these measures. (Mirabelli et al, 2020).

Cost Analysis: The National Health Service (NHS) of the United Kingdom, which is cost conscious, performed at least two cost analysis on the use of SGLT-2 inhibitors on large scale. In one study, the NHS evaluated the long-term cost-effectiveness of an intensification strategy with SGLT-2 inhibitors (pathway 1) compared to NPH insulin (pathway 2) in patients with T2DM who were not at goal on metformin and sitagliptin. The results showed that treatment intensification with SGLT-2 inhibitors prior to NPH insulin is cost-neutral or cost-effective compared with immediate NPH insulin intensification (<u>Pawaskar et al</u>, 2019). The second study evaluated the cost of glycemic target achievement with SGLT-2 inhibitors with T2DM. The analysis suggested that in the U.K. Canagliflozin 300 mg provides the best value for money among all SGLT-2 inhibitors in terms of achieving HbA1c <7.0% when used as part of a triple therapy with metformin and sulfonylurea (<u>Evans et al</u>, 2017).

Take Home Message: Despite a few serious concerns that need monitoring of patients, overall gliflozins can be considered as Wonder Drugs, as they offer cardiovascular and renal benefits that other anti-diabetic medicines cannot offer. Since, most diabetic patients eventually develop cardiovascular and/or renal complications resulting in morbidity and mortality, the use of gliflozins either as monotherapy or in combination with other anti-diabetic drugs is bound to provide added protection in T2DM. The loss of body weight and control of blood pressure are other benefits that may improve the overall health and well-being of T2DM patients.

Disclosure: Author declared no competing interests. **References:** Citations shown in the text are hyperlinks to the corresponding publications.



Image in Public Domain

Pioneers in Medicine and Sealthcare John Edward Fogarty

Nothing happened to me when I was a kid that made me decide that medicine has to be improved. It's just that I feel that as long as people are sick, something has to be done to make them better. The government has to give most of the help, because there's no one else to give it. If kids are handicapped or sick and no one is going to try everything possible to help them, well, it just can't be that way. – John E. Fogarty, quoted in Science 135 (March 2, 1962): 715

Contributed by: Bellamkonda K. Kishore, M.D.

Vision originates in the heart, and so, lack of professional knowledge, skills and abilities is not a limitation for visionaries to advance in any field. The preeminent example of such a visionary of the highest order in global healthcare being a nonmedic and modestly educated was John E. Fogarty. This is reflected in the <u>Fogarty International Center</u> for Advanced Studies in Health Sciences at the National Institutes of Health (NIH) in Bethesda, Maryland, USA, which was established in 1968 by an Executive Order by President Lyndon B. Johnson. Over the past 50 years the Fogarty International Center has provided a lot of opportunities for foreign MDs and PhDs to undergo advanced clinical training and pursue state-of-the-art research at the NIH. Most of the trainees returned to their motherlands and helped to establish clinical training and research centers. My own career as a nephrology researcher in the United States has been greatly shaped by a Fogarty International Fellowship from 1993 to 1997. There are innumerable other MDs and PhDs who were benefitted like me with Fogarty International Fellowships.

Fogarty, born on March 23, 1913 was a third generation Irish immigrant. During the great depression he worked as bricklayer. Later in the life he entered into politics and became a Congressman (D) from Rhode Island. During the 27 years career in the House of Representatives, Fogarty was the most outspoken and vocal advocate of the NIH and the importance of medical research to improve the global healthcare. In fact, Fogarty was often referred to as the *Champion of Better Health for the Nation*. Over his years as Subcommittee Chair, appropriations for the NIH increased a thousand fold, with the bulk of the funds distributed to the nation's researchers in academic institutions, health professionals schools, and hospitals. The advances in health they and successive investigators achieved as NIH grew over the decades, with worldwide benefits on health and well-being (cited from Fogarty at 35).

During his tenure as a Congressman, John E. Fogarty sponsored or co-sponsored numerous legislations of bills that immenesely benefitted the healthcare system in the USA as well as impacted the global health care. These include, but are not limited to the Hill-Fogarty Health for Peace bill; estalishment of Administration of Aging; the National Technical Institute for the Deaf; Control of Drug Abuse; Community Mental Health Amendments; Water Pollution Control Act; Medical Complex Centers for Heart Disease; Cancer and Stroke; Medical Libriary Assistance Act.

Most of us are the direct or indirect beneficiaries of the life and mission of John E. Fogarty. He envisioned that every physician or researcher should have the opportunity to participate in the state-of-the-art clincal and medical training and the fruits of such activity should reach all corners of the world. Because of his vision, dedication and untiring efforts, today the NIH is functioning as a global hub for clinical and basic medical research and training. NIH intramural and extramural research has been instrumental in our understanding of fundamental physiological, cell biological and molecular mechanisms in health and disease condisitons, as well as in the development of new treatment modalities. Over the decades, the NIH has become the benchmark of standards in medical research and healthcare all over the world.

John E. Fogarty died of heart attack at his desk on January 10, 1967. He was a modest man who preferred to say little about himself and his motivations. Shortly after his death, his family found a prayer in his wallet by Martin de Porres, a 16th century priest who ministered to the sick and homeless in Lima, Peru, who became the America's first black saint. This may be the best hint of what ultimately moved Fogarty to the action. In December 2015, the NIH created a repository of his work The John E. Fogarty Papers. To the best of my knowledge no other Congressman has been honored by the NIH, which is the premier medical institute in the world.

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COVID-19 and Diabetes

ADA + META: From the American Diabetes Association

META is a Biomedical Research Discovery Tool that analyzes & connects millions of scientific outputs to give us a comprehensive view of how your field is evolving. Through its customizable feeds, we can easily follow developments, intersections, and emerging trends in science. The following publications using Meta-analysis were indexed by the American Diabetes Association. **Click on the journal names to access the websites of the publications**.

Burden of diabetes mellitus and its impact on COVID-19 patients: A meta-analysis of real-world evidence

Salman Hussain et al <u>Diabetes Metab Syndr</u> 2020 Aug 20

Is Diabetes Mellitus a Risk Factor for COronaVirus Disease 19 (COVID-19)? Giuseppe Pugliese et al Acta Diabetol 2020 Aug 31

Psychological Adaptive Difficulties and Their Management during COVID-19 Pandemic in People with Diabetes Mellitus

Kartik Singhai et al, <u>Diabetes Metab Syndr</u> 2020 Aug 23

Type 1 Diabetes in People Hospitalized for COVID-19: New Insights from the CORONADO Study Mathieu Wargny et al, <u>Diabetes Care</u> 2020 Aug 26

> Clinical Characteristics of Diabetic Patients with COVID-19 Alamin Alkundi et al, <u>Diabetes Res Clin Pract</u> 2020 June 10

Clinical Manifestations, Risk Factors, and Maternal and Perinatal outcomes of Coronavirus Disease 2019 in Pregnancy: Living Systematic Review and META-analysis

John Allotey et al, Brit Med J 2020 Sept 2

Effects of Hyperglycaemia on Complications of COVID-19: A Meta-Analysis of Observational Studies Ming Hui Lee et al, 2020 <u>Diabetes Obes Metab</u> 2020 Sept 1

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