

# COVID-19 AND DIABETES MELLITUS

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**UNIVERSITY OF RIJEKA  
FACULTY OF MEDICINE**

**INTEGRATED UNDERGRADUATED AND GRADUATED UNIVERSITY STUDY  
OF MEDICINE IN ENGLISH**

**Florian Andreas Jungheim**

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**GRADUATION THESIS**

**Rijeka, 2023**

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## List of abbreviations

ACE2	Angiotensin-converting enzyme 2
AGEs	Advanced glycation end products
aHR	Adjusted hazard ratio
AKI	Acute kidney injury
AMP	Adenosine monophosphate
ARBs	Angiotensin II receptor blockers
ARDS	Acute respiratory distress syndrome
BMI	Body Mass Index, Body Mass Index
CCL	C-C motif chemokine ligand
CGM	Continuous glucose monitoring
CKD	Chronic kidney disease
CMV	Cytomegalovirus
COVID-19	Coronavirus disease 2019
CRP	C-reactive protein
DKA	Diabetic ketoacidosis
DM	Diabetes mellitus
DM1	Diabetes mellitus type 1
DM2	Diabetes mellitus type 2
DPP4	Dipeptidyl peptidase-4
DPP4is	Dipeptidyl peptidase-4 inhibitors
eGFR	Estimated glomerular filtration rate
ER	Endoplasmic reticulum
ESR	Erythrocyte sedimentation rate
FBS	Fasting blood sugar
FFA	Free fatty acids
GI	Gastrointestinal
GLP-1	Glucagon-like peptide-1
GLP-1-RA	Glucagon-like peptide-1 receptor agonists
GM-CSF	Granulocyte-macrophage colony-stimulating factor
hCoV-EMC	Human coronavirus-Erasmus Medical Center
HHS	Hyperosmolar hyperglycemic state

HIV	Human immunodeficiency virus
HSV	Herpes simplex virus
IAPP	Islet amyloid polypeptide
ICU	Intensive care unit
IDF	International Diabetes Federation
IFN	Interferon
IL	Interleukin
IoT	Internet of things
IR	Insulin resistance
MG	Methylglyoxal
MHC	Major histocompatibility complex
MOF	Multiple organ failure
NK cells	Natural killer cells
NRP-1	Neuropilin 1
PPAR	Peroxisome proliferator-activated receptor
PTSD	Post-traumatic stress disorders
RAAS	Renin-angiotensin-aldosterone system
RBD	Receptor binding domain
ROS	Reactive oxygen species
SGLT2i	Sodium glucose-linked transporter 2 inhibitors
s-TNF-R	Soluble TNF receptor
TG	Triglycerides
TMPRSS2	Transmembrane serine protease 2
TNF $\alpha$	Tumor necrosis factor- $\alpha$
VOC	Variants of concern
WBCs	White blood cells



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# **1 Introduction**

## **1.1 COVID-19 – Epidemiology**

The World Health Organization (WHO) has observed the recurrent emergence of different viral epidemics within the last few years. Since Coronavirus disease 2019 (COVID-19) was declared as an intercontinental pandemic by the WHO on March 11, 2020, there are more than 600 million confirmed cases of infections with the Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and more than 6.5 million globally reported deaths. (1,2) Meanwhile, multiple SARS-CoV-2 variants of concern (VOC) have spread to more than 200 countries. Known VOC in September 2022 are Alpha (B.1.1.7 lineage), Beta (B.1.351 lineage), Gamma (P.1 lineage), Delta (B.1.617.2 lineage), and the newest fifth variant Omicron (B.1.1.529 lineage). (3)

COVID-19 can affect all age cohorts. However, older individuals and those with underlying medical conditions are of higher endangerment and more often present with severe disease courses. Individuals with underlying medical conditions were described to have six times higher incidences of hospitalization than those without (45.4% vs. 7.6%) and a twelve times higher risk of dying from COVID-19 (19.5% vs. 1.6%). (4) Recent studies described an increased risk for severe disease courses and elevated mortality rates among male patients. (5)

A study of 300.000 hospitalized COVID-19 patients displayed a disparity in different racial and ethnic groups, whereby minorities had a higher hospitalization rate in comparison to white patients. (6) The highest rates of COVID-19-related deaths were seen in Hispanics. (7) Adults of a sexual minority were revealed to have an elevated risk of developing severe disease courses compared to heterosexual individuals. (8)

## **1.2 COVID-19 – Pathophysiology**

SARS-CoV-2 consists of four main structural proteins: spike (S), envelope (E), nucleocapsid (N), and membrane (M) proteins. Additionally, 16 nonstructural and 5-8 accessory proteins are known components of SARS-CoV-2. (9)

The spike (S) protein is mainly responsible for entering the host cell. It is cleaved into an amino (N)-terminal S1 subunit and a carboxyl (C)-terminal S2 subunit. The S1 subunit possesses a receptor binding domain (RBD) attaching to the human angiotensin-converting enzyme 2

(ACE2) receptor. A second component of the S1 subunit is the N-terminal domain which serves as a potential target for neutralization in response to antisera or vaccines. (10)

The fusion peptide, the transmembrane domain, and the cytoplasmic domain, all components of the S2 subunit, mediate the coalescence of the virus and the host cell. (11)

The ACE2 receptor plays a substantial role in the pathogenesis of COVID-19 since it is the S1 protein binding site of SARS-CoV-2. ACE2 receptors can be found within the respiratory, gastrointestinal (GI), hepatobiliary, cardiovascular, renal, and central nervous system. (12)

After the attachment of the spike protein (S1) RBD to the ACE2 receptor, the host transmembrane serine protease 2 (TMPRSS2) invokes the spike protein S2 subunit, and thereby the process of viral cell entry, replication, endocytosis, and virion assembling. (13)

As COVID-19 is primarily a viral respiratory disease, the pathogenesis of pneumonia must be illuminated. SARS-CoV-2-induced pneumonia can be discriminated into an early and late phase. The former stage is characterized by direct viral damage caused by its replication. In contrast, the latter stage consists of an immune response including T lymphocytes, monocytes, and neutrophils that evoke cytokine release. Cytokines playing a significant role in SARS-CoV-2 induced pneumonia are: tumor necrosis factor- $\alpha$  (TNF  $\alpha$ ), granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin (IL)-1, IL-1 $\beta$ , IL-6, IL-8, IL-12 and interferon (IFN)- $\gamma$ . Severe forms of COVID-19 can induce a massive release of cytokines resulting in local and systemic inflammatory responses. (14) Increased vascular permeability and subsequent development of pulmonary edema are results of endotheliitis caused by direct viral injury and perivascular inflammation, dysregulation of the renin-angiotensin-aldosterone system (RAAS) due to massive consumption of ACE2 receptors, activation of kallikrein-bradykinin pathways enhancing vascular permeability and enhanced epithelial cell contraction disrupting intercellular junctions. (15,16)

Extrapulmonary organ systems are damaged by either one type or different combinations of direct viral toxicity, ischemic injuries caused by vasculitis, thrombosis or thrombo-inflammation, immune dysregulation, or RAAS dysregulation. (17)

### **1.3 Diabetes mellitus type 2 – Epidemiology**

The International Diabetes Federation (IDF) in 2021 states a total number of 537 million cases of Diabetes mellitus (DM) in the age group of 20-79 years, of which more than 90% suffer from Diabetes mellitus type 2 (DM2). This number is estimated to increase to 643 million by 2030 and more than 783 million affected individuals by 2045. Developing countries show a four times higher prevalence of new cases than developed countries, with a predicted 94% rise of new DM cases until 2045 in low and middle-income countries. (18) Reasons for this phenomenon are the adaption of “western lifestyles” and the increase in the number of people with obesity in the general population. The continuous increase in the world population (expected to rise by 20% until 2045) will lead to a further rise in new DM cases. (19) The average onset of DM2 differs in developing countries, with a median onset of over 60 years, from developed nations, with an average disease onset of 40-60 years. However, there is generally a higher incidence of cases in older age groups (2.2% within the age of 20-24 years vs. 24% within 75-79 years of age). (18) In recent years, there has been a trend towards the increased occurrence of DM2 in childhood. This can be explained by either the misdiagnosis of DM2 as Diabetes mellitus type 1 (DM1) or the increased incidence of youth-onset DM2 in populations which have a higher predisposition towards the development of DM2, as its seen in Canadian first nations, American Indian, Aboriginals and African American with a general incidence of 31-94/100.000 per year versus an incidence of 0.1-0.8/100.000 per year in non-Hispanic Caucasian populations. (18). Interestingly, populations with a low rate of childhood obesity show a higher incidence of childhood DM2 compared to countries dealing with high numbers of children with obesity. Causes are thought to be a genetic predisposition towards DM2, disparities in social-economic status and access to health care, and different cultural practices. (19) DM is slightly more prevalent in males (10.8%) than in females (10.2%). (18) While the Middle East and North Africa present the regions with the highest number of DM cases, with a prevalence of 18.1% and a tendency to go up to 20.4% until 2045, African has the lowest majority, with 5% suffering from DM in the general population. The most significant number of DM cases is seen in China, followed by India and Pakistan, whereas Pakistan (30.8%), French Polynesia (25.2%), and Kuwait (24.9%) have the highest prevalence of DM in the general population. (18)

Table 1: Estimated total number of adults with Diabetes mellitus in 2021, 2030, and 2045.

	2021	2030	2045
Total world population	7.9 billion	8.6 billion	9.5 billion
Adult population (20-79 years)	5.1 billion	5.7 billion	6.4 billion
Diabetes mellitus (20-79 years)			
Prevalence	10.5%	11.3%	12.2%
Number of people with Diabetes mellitus	536.6 million	642.7 million	783.2 million

Source: Based on *IDF Atlas 10<sup>th</sup> Edition 2021.pdf* [Internet], [cited 2022 Oct 7]. Available from: [https://diabetesatlas.org/idfawp/resource-files/2021/07/IDF\\_Atlas\\_10th\\_Edition\\_2021.pdf](https://diabetesatlas.org/idfawp/resource-files/2021/07/IDF_Atlas_10th_Edition_2021.pdf)

#### 1.4 Diabetes mellitus type 2 – Pathophysiology

DM2 is one of the most common metabolic disorders. It is delineated by a combination of disturbed insulin secretion from the pancreatic  $\beta$ -cells and the ineptness of insulin-sensitive tissues to respond appropriately to insulin.

Several risk factors for the development of DM2 are described and can be broken down into modifiable and non-modifiable risk factors. Non-modifiable risk factors include ethnicity, family history, and genetic predisposition. Modifiable risk factors are far more common and composed inter alia obesity, low physical activity, and an unhealthy diet. (20) Different gene loci have been itemized to enhance the risk of DM2. They are primarily associated with primary effects on insulin secretion and can be modulated by environmental factors and vice versa. (21) DM2 develops due to improper feedback loops between insulin action and secretion, leading to high blood glucose levels. Peripheral insulin resistance (IR) aggravates the process by increasing glucose production within the liver and decreasing glucose uptake into muscles, liver, and adipose tissue. (22) In general, the dysfunction of complex networks between molecular pathways and the environment leads to disturbances within the pancreatic  $\beta$ -cells. Obesity, hyperglycemia, and hyperlipidemia, all parts of the metabolic syndrome, favor IR and chronic inflammation. When genetically susceptible  $\beta$ -cells are exposed to inflammation, endoplasmic reticulum (ER) stress as well as metabolic, oxidative, and amyloid stress, there is

a potential for the resulting loss of pancreatic islet integrity. (23) These stressors can be induced by different factors. Excessive amounts of free fatty acids (FFA) and hyperglycemia lead to ER stress by activating apoptotic unfolded protein response pathways, ultimately leading to  $\beta$ -cell damage. In addition, hyperglycemia causes an increase in proinsulin and islet amyloid polypeptide (IAPP) biosynthesis within pancreatic  $\beta$ -cells. Accumulation of those components consecutively results in the production of reactive oxygen species (ROS). (24) ROS production engenders altered  $\text{Ca}^{2+}$  mobilization, fortunate proapoptotic signals, proinsulin mRNA degradation, and IL-1 $\beta$  release. These processes induce local inflammatory processes by recruiting macrophages, disrupting islet integrity and organization, and impairing cell-to-cell communication within pancreatic islet cells. This ultimately causes poor insulin and glucagon regulation, further exacerbating the already-existing hyperglycemia. (25,26)

Besides  $\beta$ -cell dysfunction, nutritional factors play a significant role in DM2 development. The western diet is considered high caloric, including large amounts of fat and carbs. These dietary components elevate blood glucose levels, the number of circulating lipoproteins, and their remnants rich in triglycerides (TG). They are prone to induce an augmentation of ROS concentration, which yields different inflammatory processes within pancreatic  $\beta$ -cells as described above. (27) Furthermore, IR is aggravated by activation of mitochondrial damage, ER stress, activation of NADPH oxidase, and superoxide production. The sum of those processes results in activation of different inflammatory pathways, long-lasting epigenetic changes and persistent expression of proinflammatory genes. (28) Additionally, high levels of FFA cause disturbances in the electron flow within the mitochondrial respiratory chain as they favor electron leakage by getting incorporated within the mitochondrial membranes. (29)

Lifestyle modifications have shown that obesity ( $\text{BMI} \geq 30 \text{ kg/m}^2$ ) is highly associated with metabolic abnormalities and concomitant IR. (30) The Kupio Ischemic Heart Disease Risk Factor Study has depicted that participants walking 2-3 hours per week have downscaled their DM2 risk by 34-56%. Benefits were described as the increased glucose uptake from plasma by 40% due to enhanced muscular blood flow and (31,32) the reduction in intra-abdominal fat, defined as a significant factor promoting IR. (33) Reduced physical activity has been shown to stimulate the release of proinflammatory molecules within the body, including IL-1, IL-6, CRP, and TNF- $\alpha$ . Those are essential factor for NF $\kappa$ B activation which induces  $\beta$ -cell inhibition and apoptosis. (31) Regular physical activity activates the production of Interleukin-1 receptor antagonist protein and soluble TNF-receptor (s-TNF-R) as well as antioxidants like glutathione which all embody anti-inflammatory effects. (34)

## **2 Aim of this thesis**

This thesis aims to analyze the current state of studies evaluating a bidirectional relationship between COVID-19 and Diabetes mellitus type 2, as well as its implication in clinical practice. In addition, this literature review is intended to provide practical recommendations based on current guidelines regarding the management of SARS-CoV-2 patients suffering from preexisting or new-onset hyperglycemia.

### **3 Influence of COVID-19 infection on Diabetes mellitus type 2**

#### **3.1 Epidemiology of COVID-19 in patients with Diabetes mellitus type 2**

Diabetes mellitus, together with hypertension and obesity, is one of the most common comorbidities seen in COVID-19 patients. (35) Numerous reviews described the incidence of DM2 in COVID-19 patients to range from 10.8-22%. (36) However, differences between countries were pointed out. While a sizeable Catalonian study among more than six million patients seek out a prevalence of 9.3% (37) a research among New York citizens depicted an incidence of 33.8% (38), and an Italian review described a frequency of 36%. (39) The Center for Disease Control and Prevention divulged an overall majority of 10.9% of DM2 cases in patients suffering from COVID-19. (35) Kumar et al. described a prevalence of 11.2% (40), close to Chinese investigations that pointed out a frequency of 9-11%. (41,42)

Preceding studies from Kulcsar et al. published in 2019 revealed that patients with DM2 are more susceptible to MERS and SARS infection. (43) A research from Wuhan conducted in 2020 showed that 21.6% of COVID-19 patients suffered from DM2 or had at least a history of hyperglycemia. Based on their blood glucose levels at hospital admission, 20.8% of SARS-CoV-2 positive persons presented with newly diagnosed DM. Hereby, the cut-off values were defined as having either a fasting blood glucose level of  $\geq 7$  mmol/L or an HbA<sub>1c</sub> value of  $\geq 6.5\%$ . This study also described that dysglycemia, defined as fasting blood glucose levels of 5.6-6.9 mmol/L or HbA<sub>1c</sub> values of 5.7-6.4%, was present in 28.4% of patients admitted to the hospital. (44) Different national health centers exemplified the mortality risk of a COVID-19 infection in DM2 patients to be 50% higher than in nondiabetic patients. (41) DM2 patients appeared to have a heightened risk for severe complications like acute respiratory distress syndrome (ARDS) or multiple organ failure (MOF). (45) The age distribution of DM2 in COVID-19 patients tends to older age, as it was described by Kumar et al. (40) Multiple research described an increased tendency of DM2 patients towards the development of diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state after acquiring a COVID-19 infection. A study conducted on 35 patients in London described the incidence of diabetic ketoacidosis as 31.3%, mixed diabetic ketoacidosis, and the hyperosmolar hyperglycemic state as 31.7% and hyperglycemic ketoacidosis as 25.7% of which 80% of the above-described conditions were associated with DM2 diagnosed patients. (46) New-onset DM in patients who got infected with SARS-CoV-2 was reported in 20.8% of cases based on their fasting blood



glucose levels at the time of admission ( $\geq 7$  mmol/L) or their HbA<sub>1c</sub> values ( $\geq 6.5\%$ ). (44)

Another study proclaimed the incidence of new-onset DM to be 14.4%. (45)

### **3.2 Metabolic, inflammatory, and immune pathways in COVID-19 infection and Diabetes mellitus type 2**

COVID-19 infection is linked to a release of many distinct pro-inflammatory cytokines, including TNF, IL-1 $\beta$ , IL-6, C-C motif chemokine ligand (CCL)-2, CCL-3 and CCL-5 as well as hyperglycemic hormones like catecholamines and glucocorticoids. The latter two are known to be associated with rises in blood glucose levels. (47) Iatrogenic implementation of corticosteroids (e.g., Dexamethasone), as it is often seen in COVID-19 infection, can exacerbate glycemic control in short- and long-term hyperglycemic patients. (48) It is theorized that hyperglycemic patients have an already primed cytokine response which is further augmented by SARS-CoV-2 infection. This exacerbation results in a cytokine storm known as the principal factor for severe COVID-19 outcomes, namely serious pneumonia, MOF, and death. (49) High basal rates of cytokine secretion are attributed to the intensified formation of advanced glycation end products (AGEs) in patients with inadequately regulated hyperglycemia. (50) Massive cytokine release in combination with an inflammatory state can engender IR and  $\beta$ -cell dysfunction. The postulated mechanisms resulting in IR are, on the one hand, the inhibition of insulin-stimulated glycogen synthesis as well as the disturbed glucose uptake into skeletal muscle and liver cells and, on the other hand, the inhibition of lipogenesis in adipose tissue. These factors ultimately lead to hyperglycemia and IR. (51)

Specific importance in diabetic patients was attributed to IL-6, which is superior to nondiabetic patients. Since IL-6 is a pleiotropic cytokine and the primary trigger for cytokine storms, it was utilized to predict COVID-19 progression. (52) IL-6 fosters endothelial derangement leading to hypercoagulability and increased vascular permeability, conducting fluid shift and, ultimately, the development of edema. (53,54) As a consequence of hyperglycemia, patients with DM2 present with an already impaired immune response characterized by disturbed T-cell function, reduced number of polymorphonuclear leukocytes, impaired macrophage function, diminished neutrophil chemotaxis and increased adherence of microorganisms, which altogether grow the virulence of SARS-CoV-2. (48,55) The phenomenon of increased viral replication in patients with DM2 is demonstrated by monocytes, where hyperglycemia and glycolysis-mediated intramitochondrial ROS production leads to activation of hypoxia-inducible factor 1 $\alpha$ , resulting

in elevated levels of viral replication. (56) Diabetic patients also present with immune glycation damages, which decreases the expression of major histocompatibility complex (MHC) class I within myeloid cells as well as it induces raised levels of methylglyoxal (MG). MG is a known suppressor of myeloid cells and inhibitor of T-cell proliferation whereby it influences their activity towards SARS-CoV-2 antigens. (57,58) Besides suppressing T-cells, there is also a phenotypical shift of CD4<sup>+</sup> T cells towards the proinflammatory Th1, Th17, and CD8<sup>+</sup> T cell phenotypes. This alteration decreases the total number of peripheral unconventional T cells in DM2 patients. The described conversion has been demonstrated to reduce insulin sensitivity and facilitates systemic IR. (59) It is well known that expression and production of anti-inflammatory factors like IL-10, IFN- $\gamma$  and TNF are impeded by glycosylation resulting in a constant low-grade inflammation in DM2 patients. (58) Studies avowed that HbA<sub>1c</sub> levels correlated with the activity of natural killer cells (NK cells). Whereby low NK cell activity was seen in diabetic and prediabetic patients. (60) Acute and long-term hyperglycemia have been associated with changes in sorbitol, pentose phosphate, and protein kinase C pathways resulting in oxidative stress promoting endothelial cell apoptosis and subsequent endothelial dysfunction. (61) Chronic endothelial dysfunction increases the chance of severe COVID-19 infections by inducing modifications within glycocalyx and endothelial cells. These changes increase endothelial leukocyte adhesion and encourage pro-coagulation and antifibrinolytic states, ultimately resulting in endothelial and microcirculatory deterioration, promoting progression towards ARDS and MOF. (62) As a result of chronic platelet activation as well as relative inhibition of fibrinolysis, DM2 patients present with an increased susceptibility towards the development of hypercoagulable prothrombotic states. (63) This aspect was underlined by elevated levels of D-Dimers observed during COVID-19 infection. (64) SARS-CoV-2 can directly target endothelial cells via their ACE2 receptor. (65–67) Endothelial cell infection leads to the release of proinflammatory cytokines contributing to immune-mediated damages in terms of vasculitis and endotheliitis. According to the involved organ system, different presentations range from mild to severe conditions like ARDS or MOF. (68–70) The ACE2 receptor is avowed to play a vital role in the development of SARS-CoV-2 infection. Together with the protease TMPRSS2, it's a cellular receptor for virus passageway into the host cell. (71) TMPRSS2 cleaves the S1 and S2 domain of the spike protein, releasing the spike fusion peptide. The spike fusion peptide is decisive in entering the endosomal pathway and the host cell. (72) DM2 patients presented with increased levels of ACE2 receptors and TMPRSS2 which might favor SARS-CoV-2 infection. (73) The affinity of SARS-CoV-2 towards the ACE2 receptor is 10-20 times higher and associated with a lower viral clearance compared to that of SARS-CoV-

1. This is because the furin-like cleavage site (682RRAR/S686) was inserted within the S1/S2 protease cleave site of SARS-CoV-2. (74–76) It was affirmed that DM2 patients presented with higher levels of furin several years before their diagnosis. Furin is a protease that acts on the ACE2 receptors, promoting viral entry into the host cell. (77) Additional factors influencing the entry of SARS-CoV-2 into a host cell are the cytosolic pH which is lower in DM2 patients and aids in viral entry.

Moreover, SARS-CoV-2 uses the cellular metabolism of the host cell to facilitate the production of viral proteins which induces additional changes in extracellular acidification, further influencing glucose metabolism and, thereby, the production of ATP as a source of cellular energy. (71,78) ACE2 is a constituent of the RAAS system. Its function is the activation of angiotensin I-IX and I-VII, which rectify vasoconstriction and inflammatory effects of angiotensin II. (79,80) SARS-CoV-2 endocytosis into the host cell reduces ACE2 activity, shifting the balance from angiotensin I-VII towards angiotensin II, which may induce lung pathology. (81) Due to the decreased Angiotensin II degradation by ACE2, there is a resulting elevation of circulatory aldosterone and consecutive hypokalemia. (82) It has been postulated that increased levels of angiotensin II result in decreased tissue blood flow, impaired insulin signaling, and reduced insulin secretion. These factors result in reactive gluconeogenesis, glycogenolysis, and lipolysis, further enhancing IR and increasing blood glucose levels. (51) ACE2 receptors are expressed in various tissues, including pancreatic  $\beta$ -cells, lung alveolar cells, and adipose tissue, but also on cardiomyocytes, hepatocytes, enterocytes, and renal cells. (48) Current investigations assume that DM2 patients present with a raised expression of ACE2 receptors, making them more vulnerable to infections and resulting complications. (83) The expression is considered exceptionally high in the early stages of DM, with a progressive decrease over time. (84–86) ACE2 receptor expression is stimulated by acute hyperglycemia, which promotes viral entry. Increased activity of urinary ACE2 expands the viral load, as seen in DM2 patients presenting with proteinuria and a positive correlation of urinary ACE2/creatinine ratio towards fasting blood glucose and HbA<sub>1c</sub> levels. In contrast, chronic hyperglycemia causes downregulation of ACE2 receptor expression and makes cells more vulnerable to viral inflammatory effects. (45,87,88)

Liu et al. reported that 17% of COVID-19 patients presented with elevated levels of pancreatic amylases and lipases, suggesting that SARS-CoV-2 could directly damage pancreatic  $\beta$ -cells via their ACE2 receptors. (89,90) This presumption was supported by autopsy findings displaying degeneration of pancreatic islet cells in patients who succumbed to COVID-19. (91) Other postmortem investigations showed that SARS-CoV-2 was present and replicated within

pancreatic  $\beta$ -cells. There was a reduction of secretory granules responsible for insulin release and impairments in glucose-dependent insulin secretion. (92) By disturbing pancreatic islet cells' structural and functional integrity, SARS-CoV-2 may worsen preexisting DM2 or influence at least its development. (49) High mobility group box 1 (HMBG1) and Neuropilin 1 (NRP-1) are proteins of crucial importance in arbitrating the infectious potential of SARS-CoV-2. Both proteins are expressed by pancreatic islet cells. HMBG1 is a chromatin regulator critical for ACE2 receptor expression. It has been endorsed that the concentration of HMBG1 within  $\beta$ -cells of COVID-19 patients was significantly reduced. NRP-1 binds furin-cleaved substrates and thereby increases the infectivity of SARS-CoV-2. (93,94) Decreased cortisol levels in critically ill COVID-19 patients in combination with perivascular infiltrates of CD3<sup>+</sup>, and CD8<sup>+</sup> T cells were demonstrated in arterial and venous endothelial cells of the adrenal gland. This presumes that SARS-CoV-2 induces changes in carbohydrate metabolism and, ultimately, in glucose homeostasis via vascular ACE2 receptors within the adrenal gland. (95,96) In studies concerning the human coronavirus-Erasmus Medical Center (hCoV-EMC), the virus responsible for MERS, dipeptidyl peptidase-4 (DPP-4) was identified as a functional receptor for the virus. DPP-4 is a widely expressed type II transmembrane glycoprotein that plays a significant role in glucose and insulin metabolism as well as it increases inflammation in DM2 patients. (45) Antibodies against DPP-4 have been shown to inhibit the hCoV-EMC. (97) Currently, the role of DPP-4 inhibitors in SARS-CoV-2 has yet to be fully discovered. However, if DPP-4 inhibitors were to reduce the concentration of DPP-4, they could provide a therapeutic intervention for COVID-19 infections. (97) An additional factor is the point of social isolation ingoing with the SARS-CoV-2 pandemic. Negative impacts on physical activity, unhealthy eating, and weight gain were described because of the quarantine measures. These aspects are known risk factors for the development of DM2 and can consequently lead to the worsening of DM2 and the increased incidence of new-onset DM in COVID-19 patients.

### 3.3 Clinical course and prognosis of COVID-19 infection in diabetic patients

The symptomatology of COVID-19 infection in patients with DM2 possesses a broad spectrum ranging from asymptomatic to severe presentations with potentially fatal outcomes. (98) Looking back on previous pandemics like the H1N1 influenza swine flu, differences in DM2 and nondiabetic patients have been described in terms of hospitalization, Intensive care unit (ICU) admission, and mortality rates. DM2 patients who acquired the H1N1 influenza virus presented with a six-times higher hospitalization rate, a 4-fold increased incidence of ICU admission, and a doubled risk for morbid outcomes. (99–101) During the MERS-CoV outbreak in 2012, the prevalence of DM2 patients was 51%, whereby 7.2-15.7% presented with a severe clinical course and 35% of the cases with a lethal outcome. (102) Comorbidities are stated to influence the progression of SARS-CoV-2 infections. By reason of, that many DM2 patients suffer from comorbidities they are exposed to a higher risk for severe COVID-19 outcomes. Assorted studies described a 57.6% prevalence of comorbidities in DM2 patients of which 56.9% presented with hypertension and 14.7% with various other cardiovascular comorbidities. (98,103) The general prevalence of DM2 patients requiring hospitalization based on COVID-19 was determined to be 12%. (104) However, the data diverged significantly in terms of different countries. While a large study from Catalonia disclosed the hospitalization rate to be 14.8% within the first month after SARS-CoV-2 infection (37), studies from China (7.4%) (105), South Korea (17.8%) (106) and among US veterans (21.2%) (107) presented with deviating prevalence. After hospitalization, the median length of ward stay was recorded to be around four days. (108) As shown in *Table 2* there weren't significant discrepancies regarding the symptoms at the time of admission, except for higher levels of blood glucose (12.6 mmol/L vs. 6.1 mmol/L) in DM2 patients when comparing them to nondiabetic patients. (108)

Table 2: Signs and symptoms among diabetic and nondiabetic COVID-19 patients.

	Nondiabetic COVID-19 patients	Diabetic COVID-19 patients	P- value
Fever	30.1%	25.2%	0.340
Dyspnea	63.9%	63.3%	0.952
Diarrhea	3.7%	1.9%	0.361
Vomiting	9.4%	4.7%	0.127
O <sub>2</sub> saturation	91.71 ± 6.88	88.01 ± 12.96	0.001

Source: Based on Estedlal A, Jeddi M, Heydari ST, Jahromi MG, Dabbaghmanesh MH. Impacts of diabetes mellitus on clinical and para-clinical parameters among COVID-19 patients. *J Diabetes Metab Disord.* 2021 Jul 14;20(2):1211–9.

Among DM2 patients, the rate of ICU admission was elevated, as demonstrated by a large study among 64,892 SARS-CoV-2 infected US veterans, of which 7% were admitted to the ICU within 30 days after the onset of SARS-CoV-2 infection. (107) Concerning mechanical ventilation and complications of SARS-CoV-2 infection in DM2 patients, Izcovich et al. ascertained that the incidence of ARDS and the requirements for invasive mechanical ventilation are 13.2% higher than those seen in nondiabetic patients. (109) Twenty percent of DM2 patients exhibited severe clinical courses in terms of pneumonia and sepsis associated with COVID-19 infection. This suggests that DM2 is a primary risk factor for developing these conditions. (110) As shown in Table 3 the incidence of severe complications has a significant tendency towards diabetic patients.

*Table 3: Comparison of the complication incidence in diabetic and nondiabetic COVID-19 patients.*

	Nondiabetic COVID-19 patients	Diabetic COVID-19 patients
Sepsis	4.8%	31.0%
ARDS	6.6%	42.4%
Cardiovascular diseases	2.6%	19.4%
Heart Failure	3.3%	29.9%
Acute kidney injury	2.2%	24.3%

*Source: Based on Alshukry A, Bu Abbas M, Ali Y, Alahmad B, Al-Shammari AA, Alhamar G, et al. Clinical characteristics and outcomes of COVID-19 patients with diabetes mellitus in Kuwait. Heliyon. 2021 Apr 5; 7(4):e06706.*

SARS-CoV-2-infected persons exhibited oxygen levels incompatible with life without dyspneic signs. Furthermore, DM2 patients presented with a diminishment of hypoxic ventilator response by more than 50% and a 1.8-times reduced ability to perceive respiratory sensations. Those results underlined that DM2 patients had lower oxygen saturation with similar incidences of dyspnea and chest CT severity parameters compared to nondiabetic patients during their course of COVID-19. (111) X-ray scores of DM2 patients with SARS-CoV-2 infection were defined to be higher compared to that of nondiabetic patients. (64)

Due to the fact that SARS-CoV-2 can bind to renal ACE2 receptors, the virus can directly damage the kidney parenchyma. As a result of long-term kidney injuries in DM2 patients, they often display lower levels of estimated glomerular filtration rate (eGFR). The average eGFR of DM2 patients is proclaimed to be 64.56 mL/min/1.73m<sup>2</sup> in comparison to an eGFR of 70.93 mL/min/1.73m<sup>2</sup> in nondiabetic patients. Additionally, higher creatinine and urea levels were identified in DM2 patients suggesting direct kidney damage by SARS-CoV-2. The incidence of acute kidney injury (AKI) in DM2 patients was declared to be 24.3% in contrast to 2.2% in nondiabetic patients. (108) As presented above, DM2 patients are more susceptible to the SARS-CoV-2 virus since they display a condition of constant low-grade inflammation. Studies identified higher CRP levels in DM2 patients suggesting a high perceptivity toward infections. (98) Especially in children, higher incidences of DKA during the pandemic (47%) compared to the pre-pandemic time (10%), along with higher HbA<sub>1c</sub> levels (13% vs. 10.4%), were found.

(112) Besides the increased incidence within children, the number of DKA at the onset of infection were higher in new-onset diabetic patients than in already diagnosed diabetic patients. (113) Because COVID-19 is often accompanied by anosmia and GI disturbances like nausea, vomiting, and diarrhea, an increased chance of reduced food intake favoring malabsorption and nutritional deficits was elucidated. (114) Since infections are associated with increased energy requirements, mismatches between nutritional intake and needs can lead to weight loss and resulting loss of muscle mass and functionality, which were described as independent predictors of the severity and outcome of COVID-19 infections. Taking into consideration that chronically ill patients often display reduced muscle mass, they are at increased risk for severe COVID-19 courses. (115,116) The Centers for Disease Control and Prevention described the risk of mortal COVID-19 outcomes as 50% higher in diabetic patients. (117) US Cohort studies demonstrated that 32% of SARS-CoV-2-associated deaths were people with known DM2. (118) This finding was nearly confirmed by another study which exhibited an incidence of 34.7%. (98) In a US veteran study, 8% of 64,891 COVID-19-infected DM2 patients died within 30 days after acquiring SARS-CoV-2 infection. They also described the average time from obtaining the SARS-CoV-2 infection until death to be in average 35.8 days. (107) After overcoming a COVID-19, there is often described a rebound state with a weight loss of 3-5 kg during the healing phase. However, within several weeks patients typically regain their weight with phases of hyperphagia. (119)

### **3.4 Factors associated with the outcome of COVID-19 infection in patients with Diabetes mellitus type 2**

The potential most crucial risk factor determining the primary outcome of a COVID-19 infection in DM2 patients was concluded to be the glycemic control and blood glucose levels at admission and during the hospital stay. (118) Antecedent studies on the H1N1 influenza pandemic demonstrated a U-shaped association between blood glucose levels and infection in terms of hospitalization. Both high and low HbA<sub>1c</sub> levels were linked to higher risks of hospitalization. (120,121) Correlating patients with an HbA<sub>1c</sub> level of 6.5-7.0% to those of  $\geq 10\%$ , the latter had a 113% vs. 61% greater risk for lethal outcomes related to COVID-19. The last HbA<sub>1c</sub> levels before SARS-CoV-2 infection displayed a linear relationship to the mortality incidence. Furthermore, low HbA<sub>1c</sub> levels were also ingoing with an elevated rate of COVID-19-related death. (118) The proportion of mortality, ICU admission, and duration of hospital



stay was demonstrated to be influenced by glycemic fluctuations during the first hospital days. These fluctuations were even higher with the application of corticosteroid therapy. (122) The usage of corticosteroids and the infection themselves both raise blood glucose levels, thereby constraining the direction of the SARS-CoV-2 condition. (36) Blood glucose levels of  $\geq 7$  mmol/L at hospital admission were an independent determinant for 28-day mortality and the development of a critical COVID-19 infection in patients who were non-critical at that time. (123,124) Not only was hyperglycemia associated with worse outcomes in DM2 patients, but it was also linked to an increased incidence of ICU admission and death in nondiabetic patients compared to those with well-regulated blood glucose levels at the time of hospital admission. (125) In vitro studies conducted on pulmonary epithelial cells exposed to high glucose levels revealed an increased significance of influenza virus infection and replication. That contributed to a poor antiviral immune response induced by hyperglycemic conditions. (126) These animal models identified that long-term exposure to the hyperglycemic surrounding is coupled to structural lung changes, including increased vascular permeability, atelectasis, and a general reduction in pulmonary function. (126,127) Fasting blood glucose levels were ascertained to be a predictive factor for a poor COVID-19 outcome. (128) The least risk was seen for fasting blood sugar (FBS) levels of 4.74-5.78 mmol/L, while the maximum risk for a lethal COVID-19 outcome was proclaimed for FBS levels of  $\geq 7$  mmol/L and/or HbA<sub>1c</sub> values  $\geq 6.5\%$ . (129) Employing this, the usage of insulin therapy significantly improved glycemic control and, thereby, the outcome of SARS-CoV-2 patients. (130) Epidemiological studies disclosed a correlation between age and the risk for severe COVID-19 outcomes among DM2 patients. Patients below the age of 70 years were more likely to die from SARS-CoV-2 infection. (118) The adjusted hazard ratio (aHR) for the age group of 18-49 years (aHR:1.5) was more extensive than that of older age groups defined as  $\geq 50$  years (aHR:1.29). (131)

The conjunction between HbA<sub>1c</sub>, BMI, and renal impairment towards COVID-19-related mortality was more potent in patients below 70 years compared to older age groups. (132) However, the age of  $\geq 70$  years was accompanied by a higher risk of in-hospital death for both diabetic and nondiabetic patients. (103) Wander et al. defined several risk factors for COVID-19-related mortality, hospitalization, and ICU admission in DM2 patients. Risk factors linked to an increased risk of hospitalization include older age ( $\geq 60$  years), black race, Hispanic ethnicity, former or current tobacco use, usage of platelet inhibitor therapy, history of hypertension, cardiovascular diseases, heart failure, and low eGFR. Risk factors associated with an increased jeopardy of ICU admission among DM2 patients include older age ( $\geq 60$  years),

black race, Hispanic ethnicity, former or current tobacco use, history of hypertension, cardiovascular disease, and heart failure, plus a low eGFR. Factors related to a higher incidence of COVID-19 morbidity were acknowledged to be male sex, older age ( $\geq 60$  years), renal impairment, non-white ethnicity, socioeconomic deprivation, previous stroke, and heart failure. (107) Furthermore, the severity of DM2 is correlated to increased mortality risk. (118) ICU and high dependency unit (HDU) admitted patients were exposed to an 23% increased risk of all-cause mortality. (131) Going deeper into the risk factors associated with COVID-19 outcomes, obesity ( $\text{BMI} \geq 30 \text{ kg/m}^2$ ) must be mentioned as an essential aspect since it's a predisposing condition for several risk factors previously described as determinants of poor COVID-19 outcomes. Obesity is an accompanied condition often seen in DM2 patients and part of the metabolic syndrome. Animal experiments have shown that ACE2 expression was significantly higher in adipose mice compared to non-adipose mice. (133) ACE2 expression was related to a subsequent prolonged viral exposure increasing the susceptibility towards SARS-CoV-2. (134,135) Additionally, visceral fat compromises a steady state of low-grade inflammation with alterations in the innate and adaptive immune system as well as imbalances in the release of inflammatory mediators (e.g., leptin) and anti-inflammatory mediators (e.g., adiponectin) making them more vulnerable to a cytokine storm. (136,137)

The BMI was defined as an independent mortality predictor. (118) 45% of COVID-19-associated deaths in DM2 patients were referred to adiposity. (138) The hospitalization rate among people with obesity and DM2 was purported to be 32%, the rate of ICU admission 41%, the need for endotracheal ventilation 43%, and the mortality 33%. (139) A three-times expanded risk for ICU admission and death was declared for patients having a BMI above  $40 \text{ kg/m}^2$ . (140) Overweighted patients also presented with an elevated risk for ventilatory failure and complications linked to mechanical ventilation. Those, as mentioned earlier, could be elucidated by the influence of increased visceral fat leading to a reduction in minute ventilation and functional reserve capacity, especially in a supine position. (45,141) There are no significant influences of over- and underweight compared to average weight in the course of SARS-CoV-2 infection. (140) The most commonly observed condition and comorbidity of DM2 is hypertension in conjunction with other cardiovascular diseases. Several studies delineated that COVID-19 infection in DM2 patients with hypertension and macro- or microvascular complications are ingoing with an increased mortality risk. (142) Pathological reviews pointed out that among DM2 COVID-19 non-survivors, 83.9% suffered from hypertension and 45.2% from cardiovascular diseases compared to 37.5% and 18.8% in nondiabetic patients. (103) DM is determined to be the leading cause of chronic kidney disease

(CKD), with a prevalence of 40% of DM2 patients among all CKD patients. (143) CKD, in terms of an eGFR of  $< 60 \text{ ml/min/1.73m}^2$ , is described to be a significant risk factor for early and in-hospital COVID-19-related deaths. (142) Therefore, it is imperative to recognize CKD in COVID-19 patients early and adjust the drug dosage to their impaired renal function. (144) Microvascular complications like diabetic retinopathy are complications of a long-term hyperglycemic state whereby the presence of retinopathy was coupled to an increased incidence of intubation, postulating that endothelial damage and dysfunction are risk factors for extreme SARS-CoV-2-associated tissue damages. (45,145) Investigations on therapeutic insulin usage described an association between insulin use and increased morbidity and mortality. (142,146) This could be attributed to the fact that DM2 patients with a need for insulin more commonly present with more severe and longer-lasting DM2 in conjunction to SARS-CoV-2-associated glucose dysregulation, further increasing the insulin needs. (147) Laboratory investigations on different inflammatory markers in diabetic COVID-19 patients revealed a marked increase in CRP, D-Dimers, ferritin, and interleukins (especially IL-6) in patients with ARDS. (103) Cytokine and chemokine levels were linearly correlated to the severity of the condition in DM2 patients and the risk of experiencing a cytokine storm. (103,148,149) Since diabetic patients compromise a hypercoagulable state, thromboembolic events like pulmonary embolism, deep venous thrombosis, stroke, and myocardial infarction were the predominant causes of COVID-19-related deaths in DM2 patients. (45,150,151) These findings were underlined by reports of high D-Dimer levels and prolonged prothrombin time in non-survivors compared to survivors. (103,152)

### **3.5 Acute diabetic complications in COVID-19-infected patients**

In 2020, Wang et al. published a research paper demonstrating elevated amylase and lipase levels in conjunction with hyperglycemia in acutely infected COVID-19 patients. These findings suggest the involvement of pancreatic tissue by SARS-CoV-2 in terms of having the potential to cause acute pancreatic injury leading to decreased levels of insulin secretion and, ultimately, the clinical presentation of acute pancreatitis. (45) In addition to pancreatic involvement SARS-CoV-2 virus can directly trigger diabetic ketoacidosis and hyperosmolar hyperglycemic state (HHS) in patients who have pre-existing DM2. (153) Since DKA is a common clinical complication of DM1, it was less commonly seen in DM2 patients. Especially high incidences of DKA were seen among children and adolescents during the pandemic. This was attributed to being caused by less medical service available for young patients since the health care system was focusing on older people, their fear of approaching the health care system, and the influence of various psychological factors. (154) Moreover, DKA and HHS presentations were more commonly seen in patients with a high BMI. (155) Another observation made in diabetic patients during SARS-CoV-2 infection was a correlation between the severity of COVID-19 infection and the need for insulin therapy in DM2 patients during acute infection. (156)

### **3.6 Long-term outcomes in diabetic patients after COVID-19 infection**

Since the COVID-19 pandemic is a relatively new healthcare threat, long-term consequences are primarily unknown and currently under investigation. However, old data on the consequences of SARS and MERS pandemics displayed an increased prevalence of post-traumatic stress disorders (PTSD) depression, and anxiety during the first six months after hospital discharge. (157) Furthermore, increased risk for developing complications like hyperlipidemia, cardiovascular abnormalities, and changes in glucose metabolism were observed and related to infection with the SARS and MERS viruses. (158) Decreased insulin sensitivity in ARDS and sepsis survivors contributed to reduced exercise capacity and derangements in lean muscle mass after overcoming severe SARS or MERS infections. Even events of rhabdomyolysis were described as extreme cases of viral infection. (45,159) In addition to the physical incapacity, the impaired sensation of hunger, and satiety were disclosed in severe cases of ARDS and other critical conditions in going with ICU stays. Those patients

also reported increased fat accumulation and resulting cardiovascular complications. (160) Long-term studies from China on SARS patients proclaimed the occurrence of metabolic disturbances twelve years after their infection. They presented with hyperlipidemia, cardiovascular abnormalities, and alterations in glucose metabolism along with hyperglycemia, hyperinsulinemia, IR, and occurrence of DM1 and DM2. This gives off the appearance that acute SARS infections have the potential to influence the development of long-term consequences. (158) A big topic concerning the long-term consequences of SARS-CoV-2 infection is contributed to the development of new-onset DM and hyperglycemia associated with COVID-19 disease, which will be described in the next chapter. Since adverse long-term effects may be permanent without clinical symptoms, these patients' follow-up must be carried out regularly.

#### **4 New-onset Diabetes mellitus and hyperglycemia associated with COVID-19 infection**

New onset DM and hyperglycemia were shown to be associated with acute SARS-CoV-2 infections. It is unknown whether COVID-19-associated DM is phenotypically Type I, Type II, or a complex subtype of DM. Suggestive findings directing the suspicion more toward Type I would be the increased number of patients presenting with the clinical picture of DKA, which could be due to SARS-CoV-2 infection-associated pancreatic  $\beta$ -cell destruction. (161)

The incidences of newly diagnosed DM (defined by fasting blood glucose levels of  $\geq 7$  mmol/L or  $\text{HbA}_{1c} \geq 6.5\%$ ) at hospital admission in patients with acute COVID-19 infection ranged from 14.4 – 20.8%. (44,45) A study from London reported new-onset DM Type 1 during the pandemic in 30 children aged 23 months to 16.8 years. Of those 30 children, 70% presented with DKA, of which 52% had a severe manifestation of DKA. They detected an 80% increase in youth new onset DM1 during the COVID-19 pandemic compared to previous years. (162) Conflicting results were published in German studies. Among data collected from 216 pediatric diabetic centers, there was no significant increase in the number of children with new onset DM1 during the early months of the pandemic. What was described, however, was an increased incidence and severity of DKA compared to the same period in previous years. (154,163) When it comes to the potential mechanisms for new-onset DM, no conclusive mechanism is known which could thoroughly explain the relationship of the SARS-CoV-2 virus and Diabetes mellitus. Multiple complex etiologies are likely interacting with each other, ultimately leading to hyperglycemia and IR. Etiologies could include impaired glucose disposal and insulin secretion, hyperglycemia, preadmission DM, stress, and steroid use during the hospital stay. (164) One explanation for the increased occurrence of new-onset DM in COVID-19 patients is the preexistence of undiagnosed DM. This could be due to the latest weight gain induced by changes in lifestyle caused by self-isolation and social distancing leading to reduced physical activity and poor diets. (164) Contemporary surveys found that 53% of participants have reduced partly or completely their preventative measures and service levels access to non-communicable diseases. This could lead to IR, triggering inflammatory pathways, and ultimately the development of new-onset DM as the WHO proposes it. (165) Adiposity was identified as the leader for impaired glucose metabolism, immune responses, and inflammation in COVID-19 patients with hyperglycemia. (166) Studies regarding the SARS-CoV-1 pandemic illustrated that hyperglycemia and new-onset DM following hospital admission were occurring more frequently than average, leading to the assumption that stress and acute illness

can induce hyperglycemia and new-onset DM. (167) Stress hyperglycemia can induce relative insulin deficiency. This leads to an increase in lipolysis, glycogenolysis, and gluconeogenesis to meet the increased energy requirements of the organism. Lipogenesis is reduced. Free fatty acids are released into the circulation. This phenomenon of stress response is also seen in patients after severe infections or myocardial infarctions. (168) It is thought that this aspect is even more potent in COVID-19 disease, where cytokine storms can strengthen the amount of circulating fatty acids. (164) Facts underlining this assumption are the findings of elevated levels of inflammatory markers, namely C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and white blood cells (WBCs), which were found to be significantly increased in patients with new-onset DM during SARS-CoV-2 infection. (44) In addition to that, hyperglycemic patients also presented with markedly elevated levels of neutrophils and D-Dimers compared to non-hyperglycemic patients. (169) Recent data from Sathish et al. showed that stress-induced new-onset DM is more common in COVID-19 patients than other pathogens causing acute viral illnesses. (45) In addition to having systemic effects on the organism, SARS-CoV-2 is also thought to have direct and indirect influences on pancreatic tissue, as it was shown for the Human immunodeficiency virus (HIV), Mumps virus, Measles virus, Cytomegalovirus (CMV), Herpes simplex virus (HSV) and the Hepatitis virus which were all able to induce acute pancreatic infections. (170) There are controversial data about the association of the SARS-CoV-2 virus towards the ACE2 receptors expressed on pancreatic  $\beta$ -cells. Since pancreatic ACE2 receptors are predominantly expressed on pancreatic ductal epithelial cells and not on endocrine cells of the pancreas, it is unlikely that COVID-19 infection of the pancreatic tissue plays a central role in the mechanism of new-onset DM following SARS-CoV-2 illness. (171) In contrast, it is more likely that COVID-19 infection is causing cytokine and acute phase reactant release. This induction could lead to systemic inflammation resulting in damage to endocrine  $\beta$ -cells of the pancreas leading to a reduction in insulin secretion and sensation. (172) This theory was underlined by computed tomography studies demonstrating enlargement and dilatation of pancreatic ducts without findings of necrotic areas within the pancreatic tissue. (90) Recent studies suggest that the SARS-CoV-2 virus can directly infect pancreatic cells, including endocrine islets and exocrine ductal cells, thereby affecting systemic insulin levels. Enhanced autoimmunity is thought to induce pancreatic  $\beta$ -cell apoptosis leading to pancreatic destruction. (173,174)

In-hospital hyperglycemia was thought to be caused iatrogenically by the application of steroids as therapeutic measure. Previous studies in 2016 on steroid use and its influence on

hyperglycemia demonstrated that 53-70% of nondiabetic patients develop hyperglycemia after administering steroids. (175) Especially, the use of Dexamethasone in patients with severe COVID-19 infections was associated with an elevated risk of developing new-onset hyperglycemia and DM, ascribing corticosteroids a specific role in the development of new-onset hyperglycemia in COVID-19 patients. (166) The condition of new-onset DM in SARS-CoV-2 patients was highly associated with virus-related complications and mortality compared to normoglycemic patients with preexisting DM. (176) They presented an increased ICU admission incidence and elevated risks for ARDS, AKI, shock, and intubation. Additionally, the duration of the hospital stay was longer in comparison to non-new onset DM patients. (44)



## **5 Treatment approach and management of Diabetes mellitus type 2 in COVID-19 patients**

### **5.1 General Approach**

For all diabetic patients, it is recommended following the WHO references concerning disease prevention. These include prevailing protective measures like regular hand washing, wearing a face mask, and reducing contacts as much as possible to allay the risk of infection.

Testing in outpatient clinics, active surveillance, and early hospitalization for SARS-CoV-2 infection is recommended to be carried out in all high-risk patients. (119) Patients administered to ICU should have regular monitoring of blood glucose levels, electrolytes, pH, ketones, and  $\beta$ -hydroxybutyrate. The therapeutic aim for plasma glucose levels is set to be within the range of 4-8 mmol/L with an HbA<sub>1c</sub> level of less than 7%. (45) Since hyperglycemia is a constituent of the metabolic syndrome, many DM2 patients suffer from comorbidities such as hypertension and dyslipidemia. Thereupon, it is recommended to continue appropriate antihypertensives and/or lipid-lowering drugs in those patients. (45) As previously explained, SARS-CoV-2 infection relies on ACE2 receptors. Accordingly, ACE inhibitors and Angiotensin II receptor blockers (ARBs) are thought to be associated with accelerated viral entry by causing increased expression of ACE2 receptors. (45) However, new studies have elucidated that SARS-CoV-2 might impair the protective ACE2/Mas receptor pathway, thereby increasing the detrimental effects of Angiotensin-2 activity. Therefore, the use of ACE inhibitors and ARBs could have a protective role against severe pulmonary injury during and after serious COVID-19. Hence, it is recommended to continue the use of ACE inhibitors and ARBs in patients already using them. (45) As for all diabetic patients, lifestyle modification as a general measure is fundamental, including regular exercises in conjunction with reducing the sedentary lifestyle to a minimum. (45) The most crucial general measure is long-term surveillance of COVID-19 patients after overcoming their infection. This measure ensures the detection of post-COVID-19 side effects as early as possible. (45)

## 5.2 Blood glucose control

As previously described, blood glucose levels have a significant impact on the course and outcome of SARS-CoV-2 infection, making blood glucose control a central point for all hospitalized COVID-19 patients, irrespective of their diabetic status. As previously described, hyperglycemic patients had a compellingly higher risk of morbidity and mortality than diabetic patients. (177) Metabolic surveillance including strict glycemic, lipid, and blood pressure measurements, should start to be intensified as early as possible and before SARS-CoV-2 infection in terms of primary prevention of severe disease outcomes. Special attention should be kept on currently nondiabetic patients with a high potential for new-onset DM associated with SARS-CoV-2. (45) A prominence should also be given to patients receiving Dexamethasone due to an increased risk for severe glucose fluctuations. (178)

The UK National Diabetes Inpatient COVID Responsive Group published Guidelines according to blood glucose levels: (179,180)

- Patients with a history of DM or blood glucose levels of  $> 12$  mmol/L can be routinely treated for DM and monitored regularly and frequently (2-4 times/h).
- If blood glucose continuously rises and remains above 12 mmol/L, or oral therapy is impossible, insulin should be considered with a target of 7-12 mmol/L.
- If blood glucose levels are  $> 15$  mmol/L, short-acting insulin should be administered subcutaneously.

## 5.3 Antidiabetic agents

As many glucose-lowering drugs influence the immune system in dealing with the infection, optimization of antidiabetic therapy in DM2 patients prior to COVID-19 is required. Besides that, antidiabetic drugs need to be optimized in patients with severe sepsis or signs of end-organ failure, as seen with SARS-CoV-2 in terms of renal or hepatic failure. (181)

The following lines will deal with different glucose-lowering drugs, their influence on COVID-19, and recommendations for their use in diseased patients.

**Metformin**, a substance of the biguanide group, reduces IR by modifying glucose metabolism. It acts via the adenosine monophosphate (AMP)-dependent phosphokinase leading to the phosphorylation of ACE2 receptors. (182) Phosphorylation results in diminished binding capacity of the receptor-binding domain of SARS-CoV-2 towards ACE2. (183) Recent meta-

analysis found clinical and statistical affirmation in reducing COVID-19-related deaths using metformin in DM2 patients. (184–186) Similar deliverables were described by a large study among 64,892 US veterans in which metformin reduced the incidence of hospitalization and mortality within 30 days of follow-up. (107) Nevertheless, metformin use is associated with an increased risk for lactic acidosis in all diabetic patients taking it prehospital. Contrary, there was no advanced risk for patients inducing metformin during their hospital stay. (187) Considering this information, studies suggest metformin and following sick day rules in severely ill hospitalized patients. Out-hospital patients are advised to continue taking their medication. After discontinuing the metformin drug, insulin is the alternative therapy of choice. (45) In addition to severe COVID-19 infections, metformin should also be stopped in hemodynamically unstable patients exhibiting hypoxia, hepatic, renal, or heart failure since these conditions present an elevated risk for the development of lactic acidosis. (45,188) Independent of SARS-CoV-2 infection, metformin is contraindicated in patients with AKI, CKD, heart insufficiency (NYHA III and IV), and chronic respiratory insufficiency since these conditions are factors provoking lactic acidosis. (182) When metformin is taken in AKI or CKD, close monitoring for side effects is indispensable. (45)

**Dipeptidyl peptidase-4 inhibitors (DPP4is)** like linagliptin or sitagliptin are transmembrane glycoproteins. They work by increasing glucose-dependent insulin secretion via the inhibition of Dipeptidyl peptidase-4 (DPP4). DPP-4 inhibition causes decreased GLP-1 breakdown, which facilitates insulin secretion. (182) DPP-4 is widely expressed within the human body and can be found in the liver, lungs, kidneys, and several immune cells. (189) Former experimental studies on MERS-CoV discovered DPP4 as a coreceptor for the MERS spike protein, whereby more severe disease presentations were found in mice with higher DPP4 expression. (190,191) Comparative studies confirm this research by presenting reduced circulating plasma levels of DPP4 in patients with MERS-CoV using DPP4is. (192) Current speculations postulate that DPP4is could decrease virulence by acting as a coreceptor for SARS-CoV-2 spike protein, thereby interfering with the viral binding. (145) Besides that, DPP4 is also expressed on the surface of several cells regulating their immune response by activating intracellular signaling. Signaling ultimately leads to the expression of chemokines and inflammatory markers. (189) Studies in the recent past demonstrated lower levels of pro-inflammatory cytokines in acutely infected COVID-19 patients taking DPP4is compared to those not taking them. (193) Taking this information and the general well toleration of DPP4is into account, Bornstein et al. advised continuing the use of DPP4is during acute SARS-CoV-2 infection. (45,188)

**Glucagon-like peptide-1 receptor agonists (GLP-1-RA)** like semaglutide or dulaglutide have direct stimulation on Glucagon-like peptide-1 (GLP-1) receptors. By acting on GLP-1 receptors, they increase glucose-dependent insulin secretion. GLP-1-RAs are known to reduce peripheral monocyte accumulation. By doing so, they mitigate macrophage-induced inflammation. This effect is considered beneficial for COVID-19 patients in terms of functional preservation of the liver and kidney. (194) Recent studies published by Wander et al. demonstrated the association of GLP1-RAs and lower incidences of hospitalization and death following 30 days post infection. (107) Besides having anti-inflammatory characteristics, GLP-1-RAs induce weight loss. By doing so, they lead to the reduction of complications associated with overweight, like the steady state of chronic inflammation and a compromised immune system. By inducing weight reduction, GLP-1-RAs bring diabetic patients into an advantageous condition prior to acquiring SARS-CoV-2 infection. This beneficial state is associated with lower incidences of severe disease courses. (195) The commonly described GI tract side effects ingoing with GLP-1-RA use have to be mentioned, which is why regular fluid and meal intake is encouraged to prevent dehydration. (45)

**Sodium glucose-linked transporter 2 inhibitors (SGLT2i)**, for instance, canagliflozin or empagliflozin, work via a reversible inhibition of sodium glucose-linked transporter 2 located within the proximal renal tubules. Renal glucose reabsorption is constrained by their inhibitory function, resulting in increased glucose excretion and osmotic diuresis. (182) SGLT2i scale down the chronic inflammatory cell infiltrates within arterial plaques. Additionally, they reduce cytokines like IL-6 and TNF- $\alpha$  via modulation of their mRNA expression. (196) SGLT2i increase intracellular lactate concentration, lowering intracellular pH values, which might reduce viral load. (56) A large study conducted on 64.892 US veterans demonstrated a decreased incidence of hospitalization and mortality within 30 days of follow-up, leading to the suspicion that SGLT2i might reduce the severity of SARS-CoV-2 infection. (107) However, especially in critically ill patients' fluid monitoring is crucial since SGLT2i are associated with disturbances in fluid balance which might lead to severe dehydration with hemodynamic disturbances. In addition to that, patients receiving SGLT2i have to be observed and screened for the development of diabetic ketoacidosis. (188,197) Furthermore, critically ill patients often present with reduced GFR resulting in a reduction of SGLT2i binding and effects. To prevent the occurrence of AKI, close monitoring of the renal function is mandatory. Due to these side effects, Bornstein et al. advocate avoiding SGLT2i therapy during respiratory illness and following sick days rules in severely ill patients. This recommendation does not include out-hospital patients.

During SGLT2 discontinuation, the treatment of choice in DM2 patients is substitution with insulin. (45)

**Sulfonylureas** like gliclazide and glimepiride work by blocking potassium channels of the pancreatic  $\beta$ -cells. Blockage of potassium channels causes calcium influx resulting in elevated insulin secretion. In addition to their pancreatic effect, they cause a reduction in hepatic gluconeogenesis and an increase in insulin sensibility. (182) Since they have the highest hypoglycemic risk of all oral antidiabetics, they should be avoided in diabetic patients during an acute SARS-CoV-2 infection. This effect is further accelerated with the use of chloroquine and hydroxychloroquine. (188)

**Thiazolidinediones**, namely pioglitazone, reduce enteral glucose reabsorption by agonizingly affecting peroxisome proliferator-activated receptor- $\gamma$  (PPAR $\gamma$ ). PPAR $\gamma$  is a nuclear receptor regulating transcription of genes involved in glucose and lipid metabolism. (198) By driving anti-inflammatory and antioxidant effects, they reduce IR and could improve COVID-19 outcomes. This statement, however, hasn't been confirmed yet. (146,199) Due to weight gain, fluid retention, and edema formation as possible side effects, Thiazolidinediones should be discontinued in hemodynamically unstable patients with hepatic or cardiac dysfunction. (56,145,200)

**Insulin** substitution should be continued in all patients using it prior to their COVID-19 disease. (45) Wander et al. identified a higher incidence of hospitalization and death among patients using insulin before acquiring SARS-CoV-2. (107) However, many patients during their COVID-19 disease presented with massively reduced levels of insulin secretion and therefore needed higher dosages of insulin substitution. (201) Especially patients receiving dexamethasone require higher dosages and should consequently receive insulin at a daily dose of 1.2-1.5 IU/kg. This dosage should be started at the time of dexamethasone initiation to prevent subsequent fluctuations in glycemic control. (119) Many COVID-19 patients present with hypokalemia during the course of the disease, making it essential to control the potassium balance regularly. Especially with the use of insulin, potassium levels should be checked periodically since initiation of insulin could aggravate hypokalemia. (201) Insulin is also the therapy of choice if other antidiabetic drugs are contraindicated during COVID-19 disease. (187)

## 5.4 Surgical treatment

Elective metabolic surgeries are recommended to be postponed during the time of SARS-CoV-2 outbreaks. Extensive invasive procedures are associated with accelerated risks of COVID-19 complications and a generally increased risk of acquiring the SARS-CoV-2 virus during the hospital stay. In addition, every surgery is associated with stress which could negatively influence a COVID-19 outcome. (202) With the use of hemostatic instruments and the pneumoperitoneum during laparoscopy, viral aerosolization can happen, exposing the staff and other patients to potential viral material. (45) Especially metabolic surgeries are associated with postoperative deficits in nutrition, which further weakens the immune and stress response regulation. (203)

## 5.5 Health-related technologies

During the COVID-19 pandemic, digitalization has speeded up rapidly, moving telemedicine in the form of continuous glucose monitoring (CGM) into the focus of new emerging techniques. CGM and telemedicine, in general, take on the role of an alternative to inpatient point-of-care blood glucose monitoring. Studies displayed that among COVID-19 patients with blood glucose levels of 5.6-19.4 mmol/L, hypoglycemic events were prevented using CGM. Gal et al. exhibited significant improvements in HbA<sub>1c</sub> levels with a mean level of  $7.2 \pm 1.3\%$  during 12 weeks in CGM patients. (204) CGM substitutes the need for invasive blood glucose testing and thereby decreases contact points of diabetic patients towards health care workers and other patients. Additionally, the mean days for hospitalization in the isolation ward and the insulin needs were significantly reduced while still having a BG level within the range of 5.6-19.4 mmol/L. (205) Besides CGM, other telemedical devices can be connected to a network known as the “Internet of things” (IoT). The IoT makes it possible to provide frequent up-to-date data to a doctor. Continuous data allows the physician to monitor the disease progression and intervene timely. (206) Foot temperature measuring devices can early alarm for diabetic foot ulcers and avoid surgeries while simultaneously reducing overall health care costs. (207) Remote consultations via telemedicine are new possibility during the times of the COVID-19 pandemic to minimize the contact of patients towards other patients and healthcare staff. (45)

## **5.6 Vaccination**

Due to their increased risk of severe COVID-19 outcomes, diabetic patients should be preferred in getting vaccinated. Particularly young patients should have precedence in vaccination because of loss of life and work years associated with isolation measures. (208) Recent studies pointed out that DM2 and hyperglycemia do not influence anti-SARS-CoV-2 neutralizing antibodies. Quite the reverse was shown at the time of hospitalization in the form of protective effects from previous vaccinations. (209)

## **5.7 Management of new-onset Diabetes mellitus following COVID-19**

Since the exact mechanism of new-onset DM following COVID-19 is unknown, it is difficult to choose specific management for patients presenting with new-onset hyperglycemia during SARS-CoV-2 infection. Initially, the approach should be focused on the treatment of acute hyperglycemia. Recognizing new-onset DM early and managing complications like DKA is vital since they are associated with worse outcomes. In this connection, insulin is the therapy of choice and often needs to be given in high dosages. (45,169) Cohort studies showed a 18.8% incidence of new-onset hyperglycemia in COVID-19 patients at hospital admission. (210) However, during a follow-up period of 140 days to 6 months, only 3.3% (211) to 4.9% (212) of those patients presented with hyperglycemia. This led to the assumption that many patients regress to normal blood glucose levels during the time of recovery. This supposition makes the acute diagnosis of new-onset DM and induction of antidiabetic therapy, except insulin, pointless. In contrast, the follow-up of these patients is much more critical in making a definitive diagnosis of new-onset DM. (164) For patients having risk factors for poor COVID-19 outcomes, namely obesity, cardiovascular and renal diseases, the use of glucose-lowering agents in long-term therapy is recommended. Particularly the use of SGLT2i and GLP-1-RAs is endorsed in DM2 patients since they have beneficial impacts on cardiovascular and renal outcomes while promoting weight loss. (213) With this, the follow-up of patients with new onset hyperglycemia and the accurate diagnosis of DM is essential. The American Diabetes Association advises using fasting blood glucose and HbA<sub>1c</sub> levels in combination with a 2-hour oral glucose tolerance test as the diagnostic approach of choice. (214) Due to the fact that COVID-19 has long-term effects on cardiovascular and kidney function, follow-up should

focus on micro- and macrovascular complications since they are also known as complications associated with hyperglycemia. (164)



## 6 Discussion

Among different studies, the incidence of COVID-19 in DM2 patients ranged from 10.8- 22%. However, most of the investigations focused their research on a national level and had disparate study designs. While some research took only the testing of hospitalized patients into account, others included outpatient and hospitalized patients. Oftentimes, no clear definitions of DM2 or new-onset DM were given. Additionally, researchers merely focused on the age and gender of diabetic persons. They neglected other factors such as the duration of DM, the time of diagnosis, the patient's BMI, the antidiabetic therapy, and the previous diabetic complications. In furtherance of more precise results, supplementary factors should be included. A broad part of the research came from the beginning of 2020. At that time, various countries approached in different manners in terms of their corona policies and, thus, their testing procedures. Considering that DM2 patients represent a much more vulnerable patient group, they were consecutively tested more frequently. Nonetheless, mostly symptomatic patients were tested for SARS-CoV-2. Therefore, probably multiple asymptomatic infections were not included in the statistics. The testing of asymptomatic people would be important to answer whether DM2 is an independent risk factor for faster and easier infections or not. In addition to that, currently, there are just retrospective studies on the topic of DM2 and COVID-19. Acute SARS-CoV-2 infection is associated with a massive release of pro-inflammatory cytokines and hyperglycemic hormones. Given that diabetic patients already suffer from constant chronic low-grade inflammation, SARS-CoV-2 can trigger additional cytokine release, ultimately resulting in a cytokine storm. This clinical phenomenon is described in several studies as the main precipitating factor for complications like MOF, severe pneumonia, and death. As a result of chronic inflammatory processes and the associated limitations in the immune response, DM2 patients are considerably more susceptible to various infections. Moreover, DM2 patients often exhibit vascular changes predisposing to hypercoagulability and vascular fluid shifts. Especially at the dawn of the pandemic, pulmonary embolisms were described as a frequent complication. This might be due to chronic platelet activation and relative inhibition of fibrinolysis in combination with diabetic vascular changes. The clinical picture of COVID-19 in DM2 patients ranged from asymptomatic to severe presentations. By this means, comorbidities were linked to increased rates of hospitalization, ICU admission, mechanical ventilation, prolonged hospitalization duration, and mortality. Setting people with DM2 side by side with nondiabetics, many DM2 patients endure comorbidities. Being comorbid could impinge the clinical course by way of different aspects, including the compromised immune

system, the hypercoagulable state, the reduction in pulmonary function, and the micro- and macrovascular changes induced by DM2. The most prevalent grievances in diabetic and nondiabetic patients were corresponding. Both groups complained about dyspnea, fever, vomiting, diarrhea, and reduced O<sub>2</sub> saturation. However, diabetic patients presented with marked incidences of severe complications, namely sepsis, ARDS, cardiovascular diseases, heart failure, and AKI, compared to nondiabetic patients. On the one hand, this could result from alterations in the immune system induced by chronic low-grade inflammatory processes. On the other hand, SARS-CoV-2 could directly target and destroy tissue parenchyma through the ACE2 receptor resulting in ARDS and AKI. Since diabetic nephropathy is the main cause of chronic kidney failure, many patients already present with impairments in kidney function preceding COVID-19. Conclusively multiple studies showed that DM2 is a risk factor for increased morbidity and mortality in SARS-CoV-2 patients, whereby the mortality risk is described to be 2-3-times higher in diabetic patients. Nonetheless, it cannot be clearly defined whether DM2 acts as an independent risk factor or if the conjunction with multiple comorbidities is responsible for the increased severity and mortality. Notwithstanding, it must be esteemed that the conduct of the study at the local level results in vast deviations regarding demographic differences. For example, the average age of the population in Italy is greater than in China, creating broad differences in the mortality rates, as older people are much more susceptible to fatal COVID-19 outcomes. Furthermore, the question should be stated whether multiple chronic comorbidities influenced the accuracy of the results in terms of hospitalization rate, ICU admission, and mortality. Likewise, COVID-19-related deaths are defined discordantly by different research groups. Some researchers took the positive PCR result as the basis of a COVID-19-related death, while others focused on the complications ensuring COVID-19 as the cause of death. Withal this influences the number of fatal SARS-CoV-2 infections and creates disparities among researchers. The foremost risk factor for severe COVID-19 outcomes in DM2 patients is glycemic control composing the blood glucose levels at the time of and during hospital admission in conjunction with the HbA<sub>1c</sub> levels. Increased numbers of hospitalization, ICU admission, and lethal outcomes for diabetic and nondiabetic patients accompanied either. Other risk factors going along with severe disease courses were described to be older age ( $\geq 60$  years), black race, Hispanic ethnicity, former or current tobacco use, usage of platelet inhibitor therapy, history of hypertension, cardiovascular diseases, heart failure, and a low eGFR. Risk factors like age, male gender, obesity, and non-white ethnicity are circumstances found in the general population and are considerable influencing factors for DM2 development. In addition, older people are often inattentive to temperature or pulmonary

function changes as well as respiratory symptoms, contracting their threshold for SARS-CoV-2 perception. This could result in late interventions and subsequent lower survival chances. Obesity was ascertained to be an additional risk factor. Conceivable due to increased ACE2 receptor expression and incessant low-grade inflammation expressed in visceral fat tissue. Studies revealed that insulin use was connected to higher incidences of hospitalization and death. However, it must be considered that patients with high insulin needs during COVID-19 presented with more severe disease courses and, therefore, a higher risk for worse disease outcomes. Especially throughout the acute COVID-19 stage, pediatric patients exhibited DKA and hyperosmolar hyperglycemic states. In conjunction with elevated levels of amylase and lipase, this context suggests that SARS-CoV-2 can directly target and infect pancreatic tissue. Explanations for the commonplace occurrence of ketoacidosis and hyperosmolar hyperglycemic state could be a combination of reduced availability of medical services for young patients during the early pandemic and the fear of getting infected during their healthcare abidance. By virtue that SARS-CoV-2 being a relatively new healthcare menace, long-term consequences are mostly unknown and currently under investigation. Data on previous SARS and MERS pandemics displayed an increased prevalence of psychiatric disorders, hyperlipidemia, cardiovascular abnormalities, and changes in glucose metabolism, implying that this could also be an abiding consequence of COVID-19. Throughout the pandemic, many cases of new-onset DM and hyperglycemia arose. Presently the phenotype isn't defined. However, indictments of high DKA prevalence raise suspicion towards DM1. In addition to that, the underlying pathophysiological mechanisms have not yet been fully understood. Nonetheless, it is most probably of multifactorial provenance. Possible contributing factors could be impaired glucose disposal and IR, hyperglycemia, preadmission DM, infirmity stress, and steroid use, whereby undiagnosed DM is presumed to be the most common aspect. Triggers also include the sedentary lifestyle along with the isolation measures during the COVID-19 pandemic. Detrimental lifestyles engender low-grade inflammation, IR, and, ultimately, new-onset DM. Also, acute conditions associated with stress and illness induce hyperglycemia and new-onset DM. Whether SARS-CoV-2 can directly trigger new-onset DM via damaging the endocrine pancreatic tissue is a hot topic and has not yet been finally investigated. On the one hand, there are more ACE2 receptors expressed on pancreatic ductal epithelial cells in correlation to endocrine pancreatic tissue. Consequently, the virus is more likely to induce global pancreatic damage, including endocrine cells. On the other hand, recent studies assume a direct infection of endocrine pancreatic and exocrine ductal cells with subsequent apoptosis of infected cells. New-onset DM was disclosed to be associated with higher rates of

complications and mortality compared to patients with preexisting DM. Due to the relatively new emergence of COVID-19, no long-term studies exist on the emanation of new-onset DM. Because of that, it is futile to prognosticate whether and how new-onset hyperglycemia will develop in the further course. Considering that many risk factors are modifiable, a fundamental part of severe disease prevention is reducing the sedentary lifestyle to a minimum. As previously elucidated, blood glucose levels significantly influence the disease course and the outcome of COVID-19, making regular blood glucose control, irrespective of the diabetic status, crucial for all hospitalized patients. By the same token regular monitoring of electrolytes, pH, ketones, and  $\beta$ -hydroxybutyrate should be carried out. In the course of SARS-CoV-2 infection, many antidiabetic agents must be optimized in terms of COVID-19-associated complications. Metformin was proclaimed to reduce hospitalization and COVID-19-related deaths if used prior to hospital admission. Consequently, it is recommended to use metformin in outpatient conditions. Hospitalized patients should receive insulin as an alternative therapy. DPP4is could diminish severe COVID-19 courses by reducing virulence via DPP4 inhibition, which acts as a coreceptor for SARS-CoV-2. In addition to that, DPP4is carries out regulatory effects on the immune responses. Hence it is recommended to continue DPP4is use.

GLP-1-RA use is endorsed before and during COVID-19 because of the reduction in peripheral monocyte accumulation. Besides, they induce weight loss contributing to an advantageous condition of DM2 patients preceding SARS-CoV-2 infection. SGLT2i have been shown to reduce cytokine release and markdown intracellular pH values. Both might influence the course of COVID-19. Furthermore, they were associated with lower percentages of hospitalization and mortality. Accordingly, there is a general recommendation in all outpatients for using SGLT2i. Due to influences on fluid balance and their potential for DKA, SGLT2i are advocated to be avoided during acute illness. Sulfonylureas have the highest hypoglycemic risk of all oral antidiabetics and are therefore not suggested for usage during acute COVID-19. Thiazolidinediones exert anti-inflammatory and antioxidant effects, which might have beneficial influences on COVID-19 outcomes. However, they are currently not endorsed for use in SARS-CoV-2 infection because of no affirmation and possible side effects. Insulin substitution should be continued in all diabetic patients before and during their COVID-19 disease. The use of Dexamethasone should always be in concomitance with insulin substitution. Withal, insulin is the therapy of choice if other antidiabetic drugs are contraindicated. Regarding new-onset DM, choosing a specific therapeutic approach is difficult since the pathophysiological mechanism and phenotype are not clearly defined and understood. Initially, the focus should be on managing acute hyperglycemia by insulin substitution. Besides that, it

is mandatory to detect the new onset hyperglycemia and accompanying complications as early as possible. With time and after overcoming COVID-19, more than 96% of patients regressed to normal blood glucose levels. Contemplate this, the acute diagnosis and induction of antidiabetic therapy, except for insulin, is pointless in cases of new-onset DM. In contrast, the follow-up of these patients is much more important in making a definitive diagnosis. For patients having additional risk factors, namely obesity and cardiovascular and renal diseases, the use of glucose-lowering agents in long-term therapy is recommended. During follow-up, an acute diagnosis should be made according to the guidelines of the American Diabetes Association, which advises the use of fasting blood glucose and HbA<sub>1c</sub> levels in combination with a 2-hour oral glucose tolerance test. Various study limitations were present in the research mentioned above. Above all, the relatively short time we have dealt with SARS-CoV-2 must be considered. In terms of that, there are relatively few studies about the bidirectional relationship between COVID-19 and DM2. In addition, those studies currently present are exclusively of short-term. Long-term studies are required to gain further insights into the association between new-onset DM and COVID-19, as well as the long-term consequences for DM2 patients after their COVID-19 infection. Moreover, it would be interesting to see the long-term difference between new-onset DM induced by COVID-19 and new-onset DM due to acute illnesses as described for patients post-myocardial infarction. In addition, further research should be done on whether hyperglycemia on hospital admission and COVID-19-associated new-onset DM differs from usual-onset DM in long-term conditions. To better understand the interrelation between COVID-19 and DM, the exact pathophysiological mechanism of SARS-CoV-2 and the influences on pancreatic  $\beta$ -cells must be determined experimentally. Hereby, especially the role of the ACE2 receptor regarding the direct tissue damage induced by SARS-CoV-2 and the influence on new-onset DM should be of particular interest. This step is essential to determine therapeutic targets for preventing and managing new-onset DM in COVID-19 patients. Most research has been conducted on the topics of DM2 or new-onset DM. However, those studies dealing with DM1 and its relationship to SARS-CoV-2 demonstrated that DM1 patients often presented with more severe disease courses than DM2 patients. Therefore, more research should be done on the topic of DM1 and COVID-19. Concerning diabetic management, it must be evaluated whether and how different medications like GLP-1-RA, metformin, SGLT2i, ACEi, or ARB influence the short-term outcomes of COVID-19 in diabetic patients. In addition, the influence of vaccination programs on SARS-CoV-2 infection rates, courses, and outcomes in DM2 patients should be investigated.

## 7 Conclusion

This research investigated the current state of studies regarding the bidirectional relationship between COVID-19 and Diabetes mellitus type 2 in conjunction with its implication in clinical practice. Besides, practical recommendations, based on current guidelines, regarding the management of SARS-CoV-2 patients suffering from preexisting or new-onset hyperglycemia were provided. Various studies displayed a different prevalence of COVID-19 in DM2 patients concluding whether there is a higher incidence of COVID-19 in DM2 or not challenging. As a result of chronic inflammatory processes and the associated limitations in the immune response, DM2 patients are considerably more susceptible to various infections. However, to solve this question precisely, the focus should have been put on the additional testing of asymptomatic diabetic patients. Nevertheless, what can be said is that DM2 is associated with more significant risks for severe COVID-19 courses and increased incidences of complications, whereby the underlying pathogenesis is multifactorial. Likely, a combination of multiple factors, including chronic inflammatory processes, a hypercoagulable state, micro- and macrovascular changes, a compromised immune system, and reduced pulmonary function predispose DM2 patients to severe complications, explaining the higher incidences of ARDS, cardiovascular diseases, heart failure, and AKI in comparison to nondiabetic patients. Severe clinical courses are associated with a higher incidence of hospitalization, ICU admission, and mortality. Nevertheless, the foremost risk factor for worse COVID-19 outcomes is glycemic control making a good antidiabetic therapy crucial for prevention of severe SARS-CoV-2 infections. The high number of new-onset hyperglycemia associated with COVID-19 is most likely due to undiagnosed DM cases before COVID-19 infection. Furthermore, the systemic infection seen in acute COVID-19, in combination with isolation measures and the sedentary lifestyle, could also be factors for the increased incidence of new-onset hyperglycemia observed in COVID-19 patients. Anyhow, it remains to be seen how those patients' long-term blood glucose values develop and whether they recess to normal levels. Acute hyperglycemia should be treated with insulin substitution to prevent complications. The fundamental part of reducing severe COVID-19 courses are preventive measures in terms of reducing the sedentary lifestyle to a minimum, regular blood glucose control, and optimal antidiabetic therapy. In addition to that, during the hospital stay, regular pH, ketones, and  $\beta$ -hydroxybutyrate analysis should take place to ensure early therapeutic interventions if needed. Therapeutic approaches should be individually adapted to the patient's status, current circumstances, and prior antidiabetic management. Drugs of choice in outpatients are metformin and SGLT inhibitors. For hospitalized patients, DPP4is and GLP-

1-RAs are the advised medications. Insulin is the alternative for all antidiabetic drugs in case of intolerance or contraindications.

Finally, many questions remain unanswered due to the relatively short time we have dealt with the COVID-19 pandemic. A fundamental part of the research should be the understanding of pathophysiological mechanisms and the bidirectional relationship between COVID-19 and Diabetes mellitus. A particular focus should be pointed on the association of SARS-CoV-2, the ACE2 receptor, and the endocrine pancreatic  $\beta$ -cells. This is the only way to identify specific factors influencing the course of COVID-19 in DM2 and develop therapeutic strategies to prevent severe COVID-19 courses.

## 8 Summary

The incidence of COVID-19 in DM2 ranged from 10.8-22%. Due to a constant chronic inflammation, as is seen in DM2 patients, they present with increased susceptibility towards SARS-CoV-2 infections. Acute COVID-19 infections are associated with a massive release of pro-inflammatory cytokines and hyperglycemic hormones, which trigger cytokine storms and potential MOF, severe pneumonia, and death. Consequences of long-standing DM2 predispose those patients to pulmonary embolisms, ARDS, sepsis, cardiovascular diseases, heart failure, and AKI, altogether resulting in higher rates of hospitalization, ICU admission, mechanical ventilation, prolonged hospitalization duration, and 2-3-times higher fatal outcomes in comparison to nondiabetic patients. The foremost risk factor for severe outcomes in DM2 patients is glycemic control. During the COVID-19 pandemic, increased incidences of DKA and hyperosmolar hyperglycemic states are detected in conjunction with elevated amylase and lipase levels. Many cases of new-onset hyperglycemia are described, whereby the specific phenotype currently isn't defined. There is a suspicion that SARS-CoV-2 can rather directly target pancreatic tissue or induce systemic infection resulting in pancreatic  $\beta$ -cells apoptosis. For managing COVID-19 in diabetic patients, prevention in terms of optimal glycemic management and a healthy diet is crucial. Based on the individual case, antidiabetic therapy should be carried out using metformin, DPP4is, GLP-1-RA, SGLT2i, and insulin. In new-onset hyperglycemia, insulin in combination with long-term surveillance is the therapy of choice.

**COVID-19, Diabetes mellitus, Management, New-onset hyperglycemia, Pathophysiology**



## 9 Literature

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## **10 Curriculum vitae**

Florian Andreas Jungheim was born on 24. September 1997 in Frankfurt am Main, Germany as the son of two physicians. From 2004 to 2008, he attended the Wilhelm-Arnoul elementary school in Moerfelden-Walldorf. In 2008 he moved to the Carl-Schurz high school in Frankfurt am Main, where he completed his school in 2016 with the receipt of his high school diploma. A few months later, in August 2016, he began an apprenticeship as a surgical assistant at the Johann Wolfgang Goethe University in Frankfurt am Main. In June 2017, he broke off his apprenticeship after receiving a place to study at the University of Rijeka in Croatia. Since October 2017, Florian Andreas Jungheim has been studying human medicine at the Medical Faculty of Rijeka in Croatia, which he will probably complete with his diploma in July 2023.