COVID-19 AND DIABETES MELLITUS

Jungheim, Florian Andreas

UNIVERSITY OF RIJEKA
FACULTY OF MEDICINE

INTEGRATED UNDERGRADUATED AND GRADUATED UNIVERSITY STUDY OF MEDICINE IN ENGLISH

Florian Andreas Jungheim

COVID-19 AND DIABETES MELLITUS

GRADUATION THESIS

Rijeka, 2023

UNIVERSITY OF RIJEKA
FACULTY OF MEDICINE

INTEGRATED UNDERGRADUATED AND GRADUATED UNIVERSITY STUDY OF MEDICINE IN ENGLISH

Florian Andreas Jungheim

COVID-19 AND DIABETES MELLITUS

GRADUATION THESIS

Rijeka, 2023

Thesis mentor: Assoc. Prof. Sanja Klobučar, MD, PhD

The graduation thesis was graded on 12.06.2023 in Rijeka, before the Committee composed of the following members:

1. Prof. Toni Valković, MD, PhD (Committee Head)

2. Assoc. Prof. Goran Poropat, MD, PhD

3. Assoc. Prof. Đurđica Cekinović Grbeša, MD, PhD

The graduation thesis contains 73 pages, 0 figures, 3 tables, 214 references.

Table of contents

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 α	Tumor necrosis factor-α
VOC	Variants of concern
WBCs	White blood cells

Table of figures

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 side 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-α (TNF α), granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin (IL)-1, IL-1β, IL-6, IL-8, IL-12 and interferon (IFN)-γ. 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_10th_Edition_2021.pdf [Internet], [cited 2022 Oct 7]. Available from: 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 β-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 β-cells. Obesity, hyperglycemia, and hyperlipidemia, all parts of the metabolic syndrome, favor IR and chronic inflammation. When genetically susceptible β-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 β-cell damage. In addition, hyperglycemia causes an increase in proinsulin and islet amyloid polypeptide (IAPP) biosynthesis within pancreatic β-cells. Accumulation of those components consecutively results in the production of reactive oxygen species (ROS). (24) ROS production engenders altered $Ca2^{+}$ mobilization, fortunate proapoptotic signals, proinsulin mRNA degradation, and IL-1β 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 β-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 β-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 (BMI ≥ 30 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-α. Those are essential factor for NFκB activation which induces β-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_{1c} 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_{1c} 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 (≥ 7 mmol/L) or their HbA_{1c} values (≥ 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-1β, 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 β-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 1α, 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 $CD4^+$ T cells towards the proinflammatory Th1, Th17, and $CD8^+$ 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-γ and TNF are impeded by glycosylation resulting in a constant low-grade inflammation in DM2 patients. (58) Studies avowed that HbA_{1c} 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 β-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_{1c} 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 β-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 β-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 β-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 $CD3^+$, and $CD8^+$ 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_2 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^2 in comparison to an eGFR of 70.93 mL/min/1.73m^2 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_{1c} 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_{1c} levels were linked to higher risks of hospitalization. (120,121) Correlating patients with an HbA_{1c} level of 6.5-7.0% to those of ≥10%, the latter had a 113% vs. 61% greater risk for lethal outcomes related to COVID-19. The last HbA_{1c} levels before SARS-CoV-2 infection displayed a linear relationship to the mortality incidence. Furthermore, low HbA_{1c} 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 ≥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 ≥7 mmol/L and/or HbA_{1c} vales ≥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 ≥50 years (aHR:1.29). (131)

The conjunction between HbA_{1c}, 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 ≥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 (≥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 (≥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 (≥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 (BMI ≥ 30 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 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 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 β-cell destruction. (161)

The incidences of newly diagnosed DM (defined by fasting blood glucose levels of ≥ 7 mmol/L or HbA_{1c} ≥ 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 β-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 β-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 β-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 β-hydroxybutyrate. The therapeutic aim for plasma glucose levels is set to be within the range of 4-8 mmol/L with an HbA_{1c} 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-α 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 β-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-γ (PPARγ). PPARγ 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_{1c} levels with a mean level of 7.2 ± 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_{1c} 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_2 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 morality. 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_{1c} 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 (≥ 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, infirmary 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 β-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_{1c} 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 β-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 β-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 β-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 β-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

1. WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020 [Internet]. [cited 2022 Sep 27]. Available from: https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020

2. WHO COVID-19 Dashboard. Geneva: World Health Organization, 2020. [Internet]. WHO COVID-19 Dashboard. Geneva: World Health Organization, 2020. [cited 2022 Sep 27]. Available from: https://covid19.who.int/table

3. Cascella M, Rajnik M, Aleem A, Dulebohn SC, Di Napoli R. Features, Evaluation, and Treatment of Coronavirus (COVID-19). In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 [cited 2022 Sep 27]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK554776/

4. Stokes EK, Zambrano LD, Anderson KN, Marder EP, Raz KM, El Burai Felix S, et al. Coronavirus Disease 2019 Case Surveillance — United States, January 22–May 30, 2020. Morb Mortal Wkly Rep. 2020 Jun 19;69(24):759–65.

5. Gebhard C, Regitz-Zagrosek V, Neuhauser HK, Morgan R, Klein SL. Impact of sex and gender on COVID-19 outcomes in Europe. Biol Sex Differ. 2020 May 25;11:29.

6. Romano SD, Blackstock AJ, Taylor EV, El Burai Felix S, Adjei S, Singleton CM, et al. Trends in Racial and Ethnic Disparities in COVID-19 Hospitalizations, by Region — United States, March–December 2020. Morb Mortal Wkly Rep. 2021 Apr 16;70(15):560–5.

7. Ahmad FB, Cisewski JA, Miniño A, Anderson RN. Provisional Mortality Data — United States, 2020. Morb Mortal Wkly Rep. 2021 Apr 9;70(14):519–22.

8. Heslin KC, Hall JE. Sexual Orientation Disparities in Risk Factors for Adverse COVID-19-Related Outcomes, by Race/Ethnicity - Behavioral Risk Factor Surveillance System, United States, 2017-2019. MMWR Morb Mortal Wkly Rep. 2021 Feb 5;70(5):149–54

9. Jiang S, Hillyer C, Du L. Neutralizing Antibodies against SARS-CoV-2 and Other Human Coronaviruses. Trends Immunol. 2020 Jun;41(6):545.

10. Song W, Gui M, Wang X, Xiang Y. Cryo-EM structure of the SARS coronavirus spike glycoprotein in complex with its host cell receptor ACE2. PLoS Pathog. 2018 Aug 13;14(8):e1007236.

11. Du L, He Y, Zhou Y, Liu S, Zheng BJ, Jiang S. The spike protein of SARS-CoV--a target for vaccine and therapeutic development. Nat Rev Microbiol. 2009 Mar;7(3):226–36.

12. Xu H, Zhong L, Deng J, Peng J, Dan H, Zeng X, et al. High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. Int J Oral Sci. 2020 Feb 24;12:8.

13. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell. 2020 Apr 16;181(2):271-280.e8.

14. Wang J, Jiang M, Chen X, Montaner LJ. Cytokine storm and leukocyte changes in mild versus severe SARS-CoV-2 infection: Review of 3939 COVID-19 patients in China and emerging pathogenesis and therapy concepts. J Leukoc Biol. 2020 Jul;108(1):17–41.

15. Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, Laenger F, et al. Pulmonary Vascular Endothelialitis, Thrombosis, and Angiogenesis in Covid-19. N Engl J Med. 2020 Jul 9;383(2):120–8.

16. Teuwen LA, Geldhof V, Pasut A, Carmeliet P. COVID-19: the vasculature unleashed. Nat Rev Immunol. 2020 Jul;20(7):389–91.

17. Coopersmith CM, Antonelli M, Bauer SR, Deutschman CS, Evans LE, Ferrer R, et al. The Surviving Sepsis Campaign: Research Priorities for Coronavirus Disease 2019 in Critical Illness. Crit Care Med. 2021 Apr 1;49(4):598–622.

18. IDF_Atlas_10th_Edition_2021.pdf [Internet]. [cited 2022 Oct 6]. Available from: https://diabetesatlas.org/idfawp/resource-files/2021/07/IDF_Atlas_10th_Edition_2021.pdf

19. Reed J, Bain S, Kanamarlapudi V. A Review of Current Trends with Type 2 Diabetes Epidemiology, Aetiology, Pathogenesis, Treatments and Future Perspectives. Diabetes Metab Syndr Obes Targets Ther. 2021 Aug;Volume 14:3567–602.

20. Hu FB, Manson JE, Stampfer MJ, Colditz G, Liu S, Solomon CG, et al. Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. N Engl J Med. 2001 Sep 13;345(11):790–7.

21. Fuchsberger C, Flannick J, Teslovich TM, Mahajan A, Agarwala V, Gaulton KJ, et al. The genetic architecture of type 2 diabetes. Nature. 2016 Aug 4;536(7614):41–7.

22. Stumvoll M, Goldstein BJ, van Haeften TW. Type 2 diabetes: principles of pathogenesis and therapy. Lancet Lond Engl. 2005 Apr 9;365(9467):1333–46.

23. Christensen AA, Gannon M. The Beta Cell in Type 2 Diabetes. Curr Diab Rep. 2019 Aug 9;19(9):81.

24. Yamamoto WR, Bone RN, Sohn P, Syed F, Reissaus CA, Mosley AL, et al. Endoplasmic reticulum stress alters ryanodine receptor function in the murine pancreatic β cell. J Biol Chem. 2019 Jan 4;294(1):168–81.

25. Halban PA, Polonsky KS, Bowden DW, Hawkins MA, Ling C, Mather KJ, et al. β-Cell Failure in Type 2 Diabetes: Postulated Mechanisms and Prospects for Prevention and Treatment. Diabetes Care. 2014 Jun;37(6):1751–8.

26. Hoang Do O, Thorn P. Insulin secretion from beta cells within intact islets: Location matters. Clin Exp Pharmacol Physiol. 2015 Apr;42(4):406–14.

27. Dali-Youcef N, Mecili M, Ricci R, Andrès E. Metabolic inflammation: connecting obesity and insulin resistance. Ann Med. 2013 May;45(3):242–53.

28. Giacco F, Brownlee M. Oxidative stress and diabetic complications. Circ Res. 2010 Oct 29;107(9):1058–70.

29. Graciano MFR, Valle MMR, Kowluru A, Curi R, Carpinelli AR. Regulation of insulin secretion and reactive oxygen species production by free fatty acids in pancreatic islets. Islets. 2011 Oct;3(5):213–23.

30. Sinha R, Dufour S, Petersen KF, LeBon V, Enoksson S, Ma YZ, et al. Assessment of skeletal muscle triglyceride content by (1)H nuclear magnetic resonance spectroscopy in lean and obese adolescents: relationships to insulin sensitivity, total body fat, and central adiposity. Diabetes. 2002 Apr;51(4):1022–7.

31. Venkatasamy VV, Pericherla S, Manthuruthil S, Mishra S, Hanno R. Effect of Physical activity on Insulin Resistance, Inflammation and Oxidative Stress in Diabetes Mellitus. J Clin Diagn Res JCDR. 2013 Aug;7(8):1764–6.

32. Ross R. Does exercise without weight loss improve insulin sensitivity? Diabetes Care. 2003 Mar;26(3):944–5.

33. Physical activity in obesity and metabolic syndrome - PMC [Internet]. [cited 2022 Oct 13]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3715111/

34. Shamsuzzaman ASM, Winnicki M, Wolk R, Svatikova A, Phillips BG, Davison DE, et al. Independent association between plasma leptin and C-reactive protein in healthy humans. Circulation. 2004 May 11;109(18):2181–5.

35. Chow N, Fleming-Dutra K, Gierke R, Hall A, Hughes M, Pilishvili T, et al. Preliminary Estimates of the Prevalence of Selected Underlying Health Conditions Among Patients with Coronavirus Disease 2019 — United States, February 12–March 28, 2020. Morb Mortal Wkly Rep. 2020 Apr 3;69(13):382–6.

36. Hartmann-Boyce J, Rees K, Perring JC, Kerneis SA, Morris EM, Goyder C, et al. Risks of and From SARS-CoV-2 Infection and COVID-19 in People With Diabetes: A Systematic Review of Reviews. Diabetes Care. 2021 Dec 1;44(12):2790–811.

37. Prieto-Alhambra D, Balló E, Coma E, Mora N, Aragón M, Prats-Uribe A, et al. Filling the gaps in the characterization of the clinical management of COVID-19: 30-day hospital admission and fatality rates in a cohort of 118 150 cases diagnosed in outpatient settings in Spain. Int J Epidemiol. 2020 Dec 1;49(6):1930–9.

38. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. JAMA. 2020 May 26;323(20):2052–9.

39. Onder G, Rezza G, Brusaferro S. Case-Fatality Rate and Characteristics of Patients Dying in Relation to COVID-19 in Italy. JAMA. 2020 May 12;323(18):1775–6.

40. Kumar A, Arora A, Sharma P, Anikhindi SA, Bansal N, Singla V, et al. Is diabetes mellitus associated with mortality and severity of COVID-19? A meta-analysis. Diabetes Metab Syndr Clin Res Rev. 2020 Jul 1;14(4):535–45.

41. Li B, Yang J, Zhao F, Zhi L, Wang X, Liu L, et al. Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. Clin Res Cardiol. 2020;109(5):531–8.

42. Yang J, Zheng Y, Gou X, Pu K, Chen Z, Guo Q, et al. Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: a systematic review and meta-analysis. Int J Infect Dis. 2020 May;94:91–5.

43. Kulcsar KA, Coleman CM, Beck SE, Frieman MB. Comorbid diabetes results in immune dysregulation and enhanced disease severity following MERS-CoV infection. JCI Insight. 2019 Oct 17;4(20):e131774.

44. Li H, Tian S, Chen T, Cui Z, Shi N, Zhong X, et al. Newly diagnosed diabetes is associated with a higher risk of mortality than known diabetes in hospitalized patients with COVID-19. Diabetes Obes Metab. 2020 Oct;22(10):1897–906.

45. Bornstein SR, Rubino F, Khunti K, Mingrone G, Hopkins D, Birkenfeld AL, et al. Practical recommendations for the management of diabetes in patients with COVID-19. Lancet Diabetes Endocrinol. 2020 Jun;8(6):546–50.

46. Armeni E, Aziz U, Qamar S, Nasir S, Nethaji C, Negus R, et al. Protracted ketonaemia in hyperglycaemic emergencies in COVID-19: a retrospective case series. Lancet Diabetes Endocrinol. 2020 Aug;8(8):660–3.

47. Ye Q, Wang B, Mao J. The pathogenesis and treatment of the `Cytokine Storm' in COVID-19. J Infect. 2020 Jun;80(6):607–13.

48. Cuschieri S, Grech S. COVID-19 and diabetes: The why, the what and the how. J Diabetes Complications. 2020 Sep;34(9):107637.

49. Berchtold LA, Prause M, Størling J, Mandrup-Poulsen T. Chapter Five - Cytokines and Pancreatic β-Cell Apoptosis. In: Makowski GS, editor. Advances in Clinical Chemistry [Internet]. Elsevier; 2016 [cited 2022 Nov 18]. p. 99–158. Available from: https://www.sciencedirect.com/science/article/pii/S0065242316300014

50. Geerlings SE, Hoepelman AIM. Immune dysfunction in patients with diabetes mellitus (DM). FEMS Immunol Med Microbiol. 1999;26(3–4):259–65.

51. Jandeleit-Dahm KAM, Tikellis C, Reid CM, Johnston CI, Cooper ME. Why blockade of the renin-angiotensin system reduces the incidence of new-onset diabetes. J Hypertens. 2005 Mar;23(3):463–73.

52. Maddaloni E, Buzzetti R. Covid-19 and diabetes mellitus: unveiling the interaction of two pandemics. Diabetes Metab Res Rev. 2020 Oct;36(7):e33213321.

53. Procoagulant Soluble Tissue Factor Is Released From Endothelial Cells in Response to Inflammatory Cytokines [Internet]. [cited 2022 Nov 18]. Available from: https://www.ahajournals.org/doi/epdf/10.1161/01.RES.0000171805.24799.fa

54. Chelazzi C, Villa G, Mancinelli P, De Gaudio AR, Adembri C. Glycocalyx and sepsis-induced alterations in vascular permeability. Crit Care. 2015;19(1):26.

55. Daryabor G, Atashzar MR, Kabelitz D, Meri S, Kalantar K. The Effects of Type 2 Diabetes Mellitus on Organ Metabolism and the Immune System. Front Immunol. 2020 Jul 22;11:1582.

56. COVID-19 and diabetes mellitus: from pathophysiology to clinical management | Nature Reviews Endocrinology [Internet]. [cited 2022 Nov 19]. Available from: https://www.nature.com/articles/s41574-020-00435-4

57. Price CL, Hassi HOSA, English NR, Blakemore AIF, Stagg AJ, Knight SC. Methylglyoxal modulates immune responses: relevance to diabetes. J Cell Mol Med. 2010 Jun;14(6b):1806–15.

58. Klekotka RB, Mizgała E, Król W. The etiology of lower respiratory tract infections in people with diabetes. Pneumonol Alergol Pol. 2015;83(5):401–8.

59. Prasad M, Chen EW, Toh SA, Gascoigne NRJ. Autoimmune responses and inflammation in type 2 diabetes. J Leukoc Biol. 2020 May;107(5):739–48.

60. Kim JH, Park K, Lee SB, Kang S, Park JS, Ahn CW, et al. Relationship between natural killer cell activity and glucose control in patients with type 2 diabetes and prediabetes. J Diabetes Investig. 2019 Sep;10(5):1223–8.

61. van den Oever IAM, Raterman HG, Nurmohamed MT, Simsek S. Endothelial Dysfunction, Inflammation, and Apoptosis in Diabetes Mellitus. Mediators Inflamm. 2010;2010:792393.

62. Kazakou P, Lambadiari V, Ikonomidis I, Kountouri A, Panagopoulos G, Athanasopoulos S, et al. Diabetes and COVID-19; A Bidirectional Interplay. Front Endocrinol. 2022 Feb 17;13:780663.

63. Patti G, Cavallari I, Andreotti F, Calabrò P, Cirillo P, Denas G, et al. Prevention of atherothrombotic events in patients with diabetes mellitus: from antithrombotic therapies to new-generation glucose-lowering drugs. Nat Rev Cardiol. 2019;16(2):113–30.

64. Guo W, Li M, Dong Y, Zhou H, Zhang Z, Tian C, et al. Diabetes is a risk factor for the progression and prognosis of COVID-19. Diabetes Metab Res Rev. 2020 Oct;36(7):e3319.

65. Hamming I, Timens W, Bulthuis M, Lely A, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J Pathol. 2004 Jun;203(2):631–7.

66. Oudit GY, Kassiri Z, Jiang C, Liu PP, Poutanen SM, Penninger JM, et al. SARS-coronavirus modulation of myocardial ACE2 expression and inflammation in patients with SARS. Eur J Clin Invest. 2009 Jul;39(7):618–25.

67. Chen L, Li X, Chen M, Feng Y, Xiong C. The ACE2 expression in human heart indicates new potential mechanism of heart injury among patients infected with SARS-CoV-2. Cardiovasc Res. 2020 Mar 30;cvaa078.

68. He L, Ding Y, Zhang Q, Che X, He Y, Shen H, et al. Expression of elevated levels of pro-inflammatory cytokines in SARS-CoV-infected ACE2+ cells in SARS patients: relation to the acute lung injury and pathogenesis of SARS. J Pathol. 2006 Nov;210(3):288–97.

69. Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, et al. Endothelial cell infection and endotheliitis in COVID-19. The Lancet. 2020 May;395(10234):1417–8.

70. Copin MC, Parmentier E, Duburcq T, Poissy J, Mathieu D. Time to consider histologic pattern of lung injury to treat critically ill patients with COVID-19 infection. Intensive Care Med. 2020;46(6):1124–6.

71. Ehrlich A, Uhl S, Ioannidis K, Hofree M, tenOever BR, Nahmias Y. The SARS-CoV-2 Transcriptional Metabolic Signature in Lung Epithelium [Internet]. Rochester, NY; 2020 [cited 2022 Nov 19]. Available from: https://papers.ssrn.com/abstract=3650499

72. Muniyappa R, Gubbi S. COVID-19 pandemic, coronaviruses, and diabetes mellitus. Am J Physiol - Endocrinol Metab. 2020 May 1;318(5):E736–41.

73. Peters MC, Sajuthi S, Deford P, Christenson S, Rios CL, Montgomery MT, et al. COVID-19–related Genes in Sputum Cells in Asthma. Relationship to Demographic Features and Corticosteroids. Am J Respir Crit Care Med. 2020 Jul 1;202(1):83–90.

74. Ji HL, Zhao R, Matalon S, Matthay MA. Elevated Plasmin(ogen) as a Common Risk Factor for COVID-19 Susceptibility. Physiol Rev. 2020 Jul 1;100(3):1065–75.

75. Barker AB, Wagener BM. An Ounce of Prevention May Prevent Hospitalization. Physiol Rev. 2020 Jul 1;100(3):1347–8.

76. Millet JK, Whittaker GR. Host cell proteases: Critical determinants of coronavirus tropism and pathogenesis. Virus Res. 2015 Apr 16;202:120–34.

77. Fernandez C, Rysä J, Almgren P, Nilsson J, Engström G, Orho-Melander M, et al. Plasma levels of the proprotein convertase furin and incidence of diabetes and mortality. J Intern Med. 2018 Oct;284(4):377–87.

78. McElvaney OJ, McEvoy NL, McElvaney OF, Carroll TP, Murphy MP, Dunlea DM, et al. Characterization of the Inflammatory Response to Severe COVID-19 Illness. Am J Respir Crit Care Med. 2020 Sep 15;202(6):812–21.

79. Ferrario CM, Trask AJ, Jessup JA. Advances in biochemical and functional roles of angiotensin-converting enzyme 2 and angiotensin-(1–7) in regulation of cardiovascular function. Am J Physiol - Heart Circ Physiol. 2005 Dec;289(6):H2281–90.

80. AlGhatrif M, Cingolani O, Lakatta EG. The Dilemma of Coronavirus Disease 2019, Aging, and Cardiovascular Disease: Insights From Cardiovascular Aging Science. JAMA Cardiol. 2020 Jul 1;5(7):747–8.

81. Kuba K, Imai Y, Rao S, Gao H, Guo F, Guan B, et al. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus–induced lung injury. Nat Med. 2005;11(8):875–9.

82. Chen D, Li X, Song Q, Hu C, Su F, Dai J, et al. Hypokalemia and Clinical Implications in Patients with Coronavirus Disease 2019 (COVID-19) [Internet]. medRxiv; 2020 [cited 2022 Nov 19]. p. 2020.02.27.20028530. Available from: https://www.medrxiv.org/content/10.1101/2020.02.27.20028530v1

83. Rao S, Lau A, So HC. Exploring Diseases/Traits and Blood Proteins Causally Related to Expression of ACE2, the Putative Receptor of SARS-CoV-2: A Mendelian Randomization Analysis Highlights Tentative Relevance of Diabetes-Related Traits. Diabetes Care. 2020 Jul;43(7):1416–26.

84. Bindom SM, Lazartigues E. The sweeter side of ACE2: Physiological evidence for a role in diabetes. Mol Cell Endocrinol. 2009 Apr 29;302(2):193–202.

85. Ye M, Wysocki J, Naaz P, Salabat MR, LaPointe MS, Batlle D. Increased ACE 2 and Decreased ACE Protein in Renal Tubules From Diabetic Mice. Hypertension. 2004 May;43(5):1120–5.

86. Wysocki J, Ye M, Soler MJ, Gurley SB, Xiao HD, Bernstein KE, et al. ACE and ACE2 Activity in Diabetic Mice. Diabetes. 2006 Jul 1;55(7):2132–9.

87. Liang Y, Deng H, Bi S, Cui Z, A L, Zheng D, et al. Urinary Angiotensin Converting Enzyme 2 Increases in Patients With Type 2 Diabetic Mellitus. Kidney Blood Press Res. 2015;40(2):101–10.

88. Cherney DZI, Xiao F, Zimpelmann J, Har RLH, Lai V, Scholey JW, et al. Urinary ACE2 in healthy adults and patients with uncomplicated type 1 diabetes. Can J Physiol Pharmacol. 2014 Aug;92(8):703–6.

89. Lisco G, De Tullio A, Giagulli VA, Guastamacchia E, De Pergola G, Triggiani V. Hypothesized mechanisms explaining poor prognosis in type 2 diabetes patients with COVID-19: a review. Endocrine. 2020;70(3):441–53.

90. Liu F, Long X, Zhang B, Zhang W, Chen X, Zhang Z. ACE2 Expression in Pancreas May Cause Pancreatic Damage After SARS-CoV-2 Infection. Clin Gastroenterol Hepatol. 2020 Aug;18(9):2128-2130.e2.

91. Yao XH, Li TY, He ZC, Ping YF, Liu HW, Yu SC, et al. [A pathological report of three COVID-19 cases by minimal invasive autopsies]. Zhonghua Bing Li Xue Za Zhi. 2020 May 8;49(5):411–7.

92. Müller JA, Groß R, Conzelmann C, Krüger J, Merle U, Steinhart J, et al. SARS-CoV-2 infects and replicates in cells of the human endocrine and exocrine pancreas. Nat Metab. 2021 Feb;3(2):149–65.

93. Steenblock C, Richter S, Berger I, Barovic M, Schmid J, Schubert U, et al. Viral infiltration of pancreatic islets in patients with COVID-19. Nat Commun. 2021 Jun 10;12:3534.

94. Wei J, Alfajaro MM, DeWeirdt PC, Hanna RE, Lu-Culligan WJ, Cai WL, et al. Genome-wide CRISPR Screens Reveal Host Factors Critical for SARS-CoV-2 Infection. Cell. 2021 Jan 7;184(1):76-91.e13.

95. Mao Y, Xu B, Guan W, Xu D, Li F, Ren R, et al. The Adrenal Cortex, an Underestimated Site of SARS-CoV-2 Infection. Front Endocrinol. 2021 Jan 8;11:593179.

96. Ioakim KJ, Sydney GI, Paschou SA. Glucose metabolism disorders in patients with adrenal gland disorders: pathophysiology and management. Hormones. 2020 Jun 1;19(2):135–43.

97. Iacobellis G. COVID-19 and diabetes: Can DPP4 inhibition play a role? Diabetes Res Clin Pract. 2020 Apr;162:108125.

98. 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.

99. Peleg AY, Weerarathna T, McCarthy JS, Davis TME. Common infections in diabetes: pathogenesis, management and relationship to glycaemic control. Diabetes Metab Res Rev. 2007;23(1):3–13.

100. Allard R, Leclerc P, Tremblay C, Tannenbaum TN. Diabetes and the Severity of Pandemic Influenza A (H1N1) Infection. Diabetes Care. 2010 Jul;33(7):1491–3.

101. Wilking H, Buda S, Lippe E von der, Altmann D, Krause G, Eckmanns T, et al. Mortality of 2009 pandemic influenza A(H1N1) in Germany. Eurosurveillance. 2010 Dec 9;15(49):19741.

102. Badawi A, Ryoo SG. Prevalence of comorbidities in the Middle East respiratory syndrome coronavirus (MERS-CoV): a systematic review and meta-analysis. Int J Infect Dis. 2016 Aug;49:129–33.

103. Clinical Characteristics and Risk Factors for Mortality of COVID-19 Patients With Diabetes in Wuhan, China: A Two-Center, Retrospective Study | Diabetes Care | American Diabetes Association [Internet]. [cited 2022 Nov 20]. Available from: https://diabetesjournals.org/care/article/43/7/1382/35585/Clinical-Characteristics-and-Risk-Factors-for

104. Barrera FJ, Shekhar S, Wurth R, Moreno-Pena PJ, Ponce OJ, Hajdenberg M, et al. Prevalence of Diabetes and Hypertension and Their Associated Risks for Poor Outcomes in Covid-19 Patients. J Endocr Soc. 2020 Jul 21;4(9):bvaa102.

105. Guan W jie, Ni Z yi, Hu Y, Liang W hua, Ou C quan, He J xing, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020 Apr 30;382(18):1708–20.

106. Burn E, You SC, Sena AG, Kostka K, Abedtash H, Abrahão MTF, et al. Deep phenotyping of 34,128 adult patients hospitalised with COVID-19 in an international network study. Nat Commun. 2020 Oct 6;11(1):5009.

107. Wander PL, Lowy E, Beste LA, Tulloch-Palomino L, Korpak A, Peterson AC, et al. Prior Glucose-Lowering Medication Use and 30-Day Outcomes Among 64,892 Veterans With Diabetes and COVID-19. Diabetes Care. 2021 Dec;44(12):2708–13.

108. Mansour A, Sajjadi-Jazi SM, Kasaeian A, Khosravi B, Sorouri M, Azizi F, et al. Clinical characteristics and outcomes of diabetics hospitalized for COVID-19 infection: a single-centered, retrospective, observational study. EXCLI J. 2020 Nov 16;19:1533–43.

109. Izcovich A, Ragusa MA, Tortosa F, Lavena Marzio MA, Agnoletti C, Bengolea A, et al. Prognostic factors for severity and mortality in patients infected with COVID-19: A systematic review. PLoS ONE. 2020 Nov 17;15(11):e0241955.

110. Pneumonia mortality, comorbidities matter? | Elsevier Enhanced Reader [Internet]. [cited 2022 Nov 20]. Available from: https://reader.elsevier.com/reader/sd/pii/S2531043719302053?token=989C4AB22B61A4475F88C43830CF9E2635700F9871351F038788E0AE49AAD8056452A8D1B3A550509422B42625139DE9&originRegion=eu-west-1&originCreation=20221120110225

111. 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.

112. McGlacken-Byrne SM, Drew SEV, Turner K, Peters C, Amin R. The SARS-CoV-2 pandemic is associated with increased severity of presentation of childhood onset type 1 diabetes mellitus: A multi-centre study of the first COVID-19 wave. Diabet Med. 2021 Sep;38(9):e14640.

113. Boddu SK, Aurangabadkar G, Kuchay MS. New onset diabetes, type 1 diabetes and COVID-19. Diabetes Metab Syndr. 2020;14(6):2211–7.

114. Gupta A, Madhavan MV, Sehgal K, Nair N, Mahajan S, Sehrawat TS, et al. Extrapulmonary manifestations of COVID-19. Nat Med. 2020 Jul;26(7):1017–32.

115. Ballesteros Pomar MD, Bretón Lesmes I. Nutrición Clínica en tiempos de COVID-19. Endocrinol Diabetes Nutr. 2020;67(7):427–30.

116. Gomes F, Schuetz P, Bounoure L, Austin P, Ballesteros-Pomar M, Cederholm T, et al. ESPEN guidelines on nutritional support for polymorbid internal medicine patients. Clin Nutr. 2018 Feb;37(1):336–53.

117. Remuzzi A, Remuzzi G. COVID-19 and Italy: what next? Lancet Lond Engl. 2020;395(10231):1225–8.

118. Holman N, Knighton P, Kar P, O'Keefe J, Curley M, Weaver A, et al. Risk factors for COVID-19-related mortality in people with type 1 and type 2 diabetes in England: a population-based cohort study. Lancet Diabetes Endocrinol. 2020 Oct;8(10):823–33.

119. Puig-Domingo M, Marazuela M, Yildiz BO, Giustina A. COVID-19 and endocrine and metabolic diseases. An updated statement from the European Society of Endocrinology. Endocrine. 2021;72(2):301–16.

120. Wang W, Chen H, Li Q, Qiu B, Wang J, Sun X, et al. Fasting plasma glucose is an independent predictor for severity of H1N1 pneumonia. BMC Infect Dis. 2011 Apr 21;11:104.

121. Luk AOY, Lau ESH, Cheung KKT, Kong APS, Ma RCW, Ozaki R, et al. Glycaemia control and the risk of hospitalisation for infection in patients with type 2 diabetes: Hong Kong Diabetes Registry. Diabetes Metab Res Rev. 2017;33(8):e2923.

122. Chen L, Sun W, Liu Y, Zhang L, Lv Y, Wang Q, et al. Association of Early-Phase In-Hospital Glycemic Fluctuation With Mortality in Adult Patients With Coronavirus Disease 2019. Diabetes Care. 2021 Apr;44(4):865–73.

123. Wang S, Ma P, Zhang S, Song S, Wang Z, Ma Y, et al. Fasting blood glucose at admission is an independent predictor for 28-day mortality in patients with COVID-19 without previous diagnosis of diabetes: a multi-centre retrospective study. Diabetologia. 2020;63(10):2102–11.

124. Wu J, Huang J, Zhu G, Wang Q, Lv Q, Huang Y, et al. Elevation of blood glucose level predicts worse outcomes in hospitalized patients with COVID-19: a retrospective cohort study. BMJ Open Diabetes Res Care. 2020 Jun;8(1):e001476.

125. Lee MH, Wong C, Ng CH, Yuen DCW, Lim AYL, Khoo CM. Effects of hyperglycaemia on complications of COVID-19: A meta-analysis of observational studies. Diabetes Obes Metab. 2021;23(1):287–9.

126. Philips BJ, Meguer JX, Redman J, Baker EH. Factors determining the appearance of glucose in upper and lower respiratory tract secretions. Intensive Care Med. 2003 Dec;29(12):2204–10.

127. López-Cano C, Lecube A, García-Ramírez M, Muñoz X, Sánchez E, Seminario A, et al. Serum Surfactant Protein D as a Biomarker for Measuring Lung Involvement in Obese Patients With Type 2 Diabetes. J Clin Endocrinol Metab. 2017 Nov 1;102(11):4109–16.

128. Zhang B, Liu S, Zhang L, Dong Y, Zhang S. Admission fasting blood glucose predicts 30-day poor outcome in patients hospitalized for COVID-19 pneumonia. Diabetes Obes Metab. 2020 Oct;22(10):1955–7.

129. Zhu B, Jin S, Wu L, Hu C, Wang Z, Bu L, et al. J-shaped association between fasting blood glucose levels and COVID-19 severity in patients without diabetes. Diabetes Res Clin Pract. 2020 Oct;168:108381.

130. Sardu C, D'Onofrio N, Balestrieri ML, Barbieri M, Rizzo MR, Messina V, et al. Outcomes in Patients With Hyperglycemia Affected by COVID-19: Can We Do More on Glycemic Control? Diabetes Care. 2020 Jul;43(7):1408–15.

131. Dennis JM, Mateen BA, Sonabend R, Thomas NJ, Patel KA, Hattersley AT, et al. Type 2 Diabetes and COVID-19–Related Mortality in the Critical Care Setting: A National Cohort Study in England, March–July 2020. Diabetes Care. 2021 Jan;44(1):50–7.

132. Desai R, Singh S, Parekh T, Sachdeva S, Sachdeva R, Kumar G. COVID-19 and diabetes mellitus: A need for prudence in elderly patients from a pooled analysis. Diabetes Metab Syndr. 2020;14(4):683–5.

133. Al Heialy S, Hachim MY, Senok A, Gaudet M, Abou Tayoun A, Hamoudi R, et al. Regulation of Angiotensin- Converting Enzyme 2 in Obesity: Implications for COVID-19. Front Physiol. 2020 Sep 18;11:555039.

134. Bourgonje AR, Abdulle AE, Timens W, Hillebrands J, Navis GJ, Gordijn SJ, et al. Angiotensin-converting enzyme 2 (ACE2), SARS-CoV-2 and the pathophysiology of coronavirus disease 2019 (COVID-19). J Pathol. 2020 Jul;251(3):228–48.

135. Moriconi D, Masi S, Rebelos E, Virdis A, Manca ML, De Marco S, et al. Obesity prolongs the hospital stay in patients affected by COVID-19, and may impact on SARS-COV-2 shedding. Obes Res Clin Pract. 2020;14(3):205–9.

136. Ryan PM, Caplice NM. Is Adipose Tissue a Reservoir for Viral Spread, Immune Activation, and Cytokine Amplification in Coronavirus Disease 2019? Obes Silver Spring Md. 2020 Jul;28(7):1191–4.

137. Andersen CJ, Murphy KE, Fernandez ML. Impact of Obesity and Metabolic Syndrome on Immunity12. Adv Nutr. 2016 Jan 7;7(1):66–75.

138. Bello-Chavolla OY, Bahena-López JP, Antonio-Villa NE, Vargas-Vázquez A, González-Díaz A, Márquez-Salinas A, et al. Predicting mortality due to SARS-CoV-2: A mechanistic score relating obesity and diabetes to COVID-19 outcomes in Mexico. J Clin Endocrinol Metab. 2020 May 31;dgaa346.

139. Helvaci N, Eyupoglu ND, Karabulut E, Yildiz BO. Prevalence of Obesity and Its Impact on Outcome in Patients With COVID-19: A Systematic Review and Meta-Analysis. Front Endocrinol. 2021 Feb 25;12:598249.

140. Treskova-Schwarzbach M, Haas L, Reda S, Pilic A, Borodova A, Karimi K, et al. Pre-existing health conditions and severe COVID-19 outcomes: an umbrella review approach and meta-analysis of global evidence. BMC Med. 2021 Aug 27;19:212.

141. Stefan N, Birkenfeld AL, Schulze MB, Ludwig DS. Obesity and impaired metabolic health in patients with COVID-19. Nat Rev Endocrinol. 2020;16(7):341–2.

142. Cariou B, Hadjadj S, Wargny M, Pichelin M, Al-Salameh A, Allix I, et al. Phenotypic characteristics and prognosis of inpatients with COVID-19 and diabetes: the CORONADO study. Diabetologia. 2020;63(8):1500–15.

143. Bailey RA, Wang Y, Zhu V, Rupnow MF. Chronic kidney disease in US adults with type 2 diabetes: an updated national estimate of prevalence based on Kidney Disease: Improving Global Outcomes (KDIGO) staging. BMC Res Notes. 2014 Jul 2;7:415.

144. Roberto P, Francesco L, Emanuela C, Giorgia G, Pasquale N, Sara D. Current treatment of COVID-19 in renal patients: hope or hype? Intern Emerg Med. 2020;15(8):1389–98.

145. Apicella M, Campopiano MC, Mantuano M, Mazoni L, Coppelli A, Del Prato S. COVID-19 in people with diabetes: understanding the reasons for worse outcomes. Lancet Diabetes Endocrinol. 2020 Sep;8(9):782–92.

146. McGurnaghan SJ, Weir A, Bishop J, Kennedy S, Blackbourn LAK, McAllister DA, et al. Risks of and risk factors for COVID-19 disease in people with diabetes: a cohort study of the total population of Scotland. Lancet Diabetes Endocrinol. 2021 Feb;9(2):82–93.

147. Landstra CP, de Koning EJP. COVID-19 and Diabetes: Understanding the Interrelationship and Risks for a Severe Course. Front Endocrinol. 2021 Jun 17;12:649525.

148. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Intern Med. 2020 Jul;180(7):1–11.

149. Petrilli CM, Jones SA, Yang J, Rajagopalan H, O'Donnell L, Chernyak Y, et al. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. The BMJ. 2020 May 22;369:m1966.

150. Lodigiani C, Iapichino G, Carenzo L, Cecconi M, Ferrazzi P, Sebastian T, et al. Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. Thromb Res. 2020 Jul;191:9–14.

151. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost. 2020 Apr;18(4):844–7.

152. Yan Y, Yang Y, Wang F, Ren H, Zhang S, Shi X, et al. Clinical characteristics and outcomes of patients with severe covid-19 with diabetes. BMJ Open Diabetes Res Care. 2020 Apr 27;8(1):e001343.

153. Li J, Wang X, Chen J, Zuo X, Zhang H, Deng A. COVID-19 infection may cause ketosis and ketoacidosis. Diabetes Obes Metab. 2020 Oct;22(10):1935–41.

154. Kamrath C, Mönkemöller K, Biester T, Rohrer TR, Warncke K, Hammersen J, et al. Ketoacidosis in Children and Adolescents With Newly Diagnosed Type 1 Diabetes During the COVID-19 Pandemic in Germany. JAMA. 2020 Aug 25;324(8):801–4.

155. Pasquel FJ, Messler J, Booth R, Kubacka B, Mumpower A, Umpierrez G, et al. Characteristics of and Mortality Associated With Diabetic Ketoacidosis Among US Patients Hospitalized With or Without COVID-19. JAMA Netw Open. 2021 Mar 10;4(3):e211091.

156. nhs-aftercarecovid.pdf [Internet]. [cited 2022 Dec 19]. Available from: https://www.pcrs-uk.org/sites/default/files/nhs-aftercarecovid.pdf

157. Zhou J, Tan J. Letter to the Editor: Diabetes patients with COVID-19 need better blood glucose management in Wuhan, China. Metabolism. 2020 Jun;107:154216.

158. Wu Q, Zhou L, Sun X, Yan Z, Hu C, Wu J, et al. Altered Lipid Metabolism in Recovered SARS Patients Twelve Years after Infection. Sci Rep. 2017 Aug 22;7:9110.

159. Rocheteau P, Chatre L, Briand D, Mebarki M, Jouvion G, Bardon J, et al. Sepsis induces long-term metabolic and mitochondrial muscle stem cell dysfunction amenable by mesenchymal stem cell therapy. Nat Commun. 2015 Dec 15;6:10145.

160. Huang M, Parker AM, Bienvenu OJ, Dinglas VD, Colantuoni E, Hopkins RO, et al. Psychiatric Symptoms in Acute Respiratory Distress Syndrome Survivors: A One-Year National Multi-Center Study. Crit Care Med. 2016 May;44(5):954–65.

161. Hollstein T, Schulte DM, Schulz J, Glück A, Ziegler AG, Bonifacio E, et al. Autoantibody-negative insulin-dependent diabetes mellitus after SARS-CoV-2 infection: a case report. Nat Metab. 2020 Oct;2(10):1021–4.

162. Unsworth R, Wallace S, Oliver NS, Yeung S, Kshirsagar A, Naidu H, et al. New-Onset Type 1 Diabetes in Children During COVID-19: Multicenter Regional Findings in the U.K. Diabetes Care. 2020 Nov 1;43(11):e170–1.

163. Tittel SR, Rosenbauer J, Kamrath C, Ziegler J, Reschke F, Hammersen J, et al. Did the COVID-19 Lockdown Affect the Incidence of Pediatric Type 1 Diabetes in Germany? Diabetes Care. 2020 Nov;43(11):e172–3.

164. Khunti K, Del Prato S, Mathieu C, Kahn SE, Gabbay RA, Buse JB. COVID-19, Hyperglycemia, and New-Onset Diabetes. Diabetes Care. 2021 Dec;44(12):2645–55.

165. COVID-19 significantly impacts health services for noncommunicable diseases [Internet]. [cited 2022 Dec 20]. Available from: https://www.who.int/news/item/01-06-2020-covid-19-significantly-impacts-health-services-for-noncommunicable-diseases

166. Accili D. Can COVID-19 cause diabetes? Nat Metab. 2021 Feb;3(2):123–5.

167. Yang JK, Feng Y, Yuan MY, Yuan SY, Fu HJ, Wu BY, et al. Plasma glucose levels and diabetes are independent predictors for mortality and morbidity in patients with SARS. Diabet Med J Br Diabet Assoc. 2006 Jun;23(6):623–8.

168. Capes SE, Hunt D, Malmberg K, Gerstein HC. Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: a systematic overview. The Lancet. 2000 Mar 4;355(9206):773–8.

169. Coppelli A, Giannarelli R, Aragona M, Penno G, Falcone M, Tiseo G, et al. Hyperglycemia at Hospital Admission Is Associated With Severity of the Prognosis in Patients Hospitalized for COVID-19: The Pisa COVID-19 Study. Diabetes Care. 2020 Oct;43(10):2345–8.

170. Rawla P, Bandaru SS, Vellipuram AR. Review of Infectious Etiology of Acute Pancreatitis. Gastroenterol Res. 2017 Jun;10(3):153–8.

171. Kusmartseva I, Wu W, Syed F, Van Der Heide V, Jorgensen M, Joseph P, et al. Expression of SARS-CoV-2 Entry Factors in the Pancreas of Normal Organ Donors and Individuals with COVID-19. Cell Metab. 2020 Dec 1;32(6):1041-1051.e6.

172. Ahlqvist E, Storm P, Käräjämäki A, Martinell M, Dorkhan M, Carlsson A, et al. Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables. Lancet Diabetes Endocrinol. 2018 May;6(5):361–9.

173. Shaharuddin SH, Wang V, Santos RS, Gross A, Wang Y, Jawanda H, et al. Deleterious Effects of SARS-CoV-2 Infection on Human Pancreatic Cells. Front Cell Infect Microbiol. 2021;11:678482.

174. SARS-CoV-2 infects human pancreatic β cells and elicits β cell impairment - PubMed [Internet]. [cited 2022 Dec 20]. Available from: https://pubmed.ncbi.nlm.nih.gov/34081912/

175. Cheung NW. Steroid-induced hyperglycaemia in hospitalised patients: does it matter? Diabetologia. 2016 Dec;59(12):2507–9.

176. Singh AK, Singh R. Hyperglycemia without diabetes and new-onset diabetes are both associated with poorer outcomes in COVID-19. Diabetes Res Clin Pract. 2020 Sep;167:108382.

177. Bode B, Garrett V, Messler J, McFarland R, Crowe J, Booth R, et al. Glycemic Characteristics and Clinical Outcomes of COVID-19 Patients Hospitalized in the United States. J Diabetes Sci Technol. 2020 May 9;14(4):813–21.

178. Rayman G, Lumb AN, Kennon B, Cottrell C, Nagi D, Page E, et al. Dexamethasone therapy in COVID-19 patients: implications and guidance for the management of blood glucose in people with and without diabetes. Diabet Med. 2021 Jan;38(1):e14378.

179. Sinclair A, Dhatariya K, Burr O, Nagi D, Higgins K, Hopkins D, et al. Guidelines for the management of diabetes in care homes during the Covid-19 pandemic. Diabet Med. 2020 Jul;37(7):1090–3.

180. Rayman G, Lumb A, Kennon B, Cottrell C, Nagi D, Page E, et al. Guidelines for the management of diabetes services and patients during the COVID-19 pandemic. Diabet Med. 2020;37(7):1087–9.

181. Lazarus G, Audrey J, Wangsaputra VK, Tamara A, Tahapary DL. High admission blood glucose independently predicts poor prognosis in COVID-19 patients: A systematic review and dose-response meta-analysis. Diabetes Res Clin Pract. 2021 Jan;171:108561.

182. Antidiabetika - AMBOSS [Internet]. [cited 2023 Jan 6]. Available from: https://next.amboss.com/de/article/7m04Sg?q=metformin+%28pharmakologie%29#Z29274f66b44cfca08fcfcd8de41b1ea0

183. Sharma S, Ray A, Sadasivam B. Metformin in COVID-19: A possible role beyond diabetes. Diabetes Res Clin Pract. 2020 Jun;164:108183.

184. Hariyanto TI, Kurniawan A. Metformin use is associated with reduced mortality rate from coronavirus disease 2019 (COVID-19) infection. Obes Med. 2020 Sep;19:100290.

185. Kow CS, Hasan SS. Mortality risk with preadmission metformin use in patients with COVID-19 and diabetes: A meta-analysis. J Med Virol. 2021;93(2):695–7.

186. Lukito AA, Pranata R, Henrina J, Lim MA, Lawrensia S, Suastika K. The Effect of Metformin Consumption on Mortality in Hospitalized COVID-19 patients: a systematic review and meta-analysis. Diabetes Metab Syndr. 2020;14(6):2177–83.

187. Flaherty GT, Hession P, Liew CH, Lim BCW, Leong TK, Lim V, et al. COVID-19 in adult patients with pre-existing chronic cardiac, respiratory and metabolic disease: a critical literature review with clinical recommendations. Trop Dis Travel Med Vaccines. 2020 Aug 28;6(1):16.

188. Drucker DJ. Coronavirus infections and type 2 diabetes-shared pathways with therapeutic implications. Endocr Rev. 2020 Apr 15;bnaa011.

189. Mulvihill EE, Drucker DJ. Pharmacology, physiology, and mechanisms of action of dipeptidyl peptidase-4 inhibitors. Endocr Rev. 2014 Dec;35(6):992–1019.

190. Raj VS, Mou H, Smits SL, Dekkers DHW, Müller MA, Dijkman R, et al. Dipeptidyl peptidase 4 is a functional receptor for the emerging human coronavirus-EMC. Nature. 2013 Mar 14;495(7440):251–4.

191. Vankadari N, Wilce JA. Emerging WuHan (COVID-19) coronavirus: glycan shield and structure prediction of spike glycoprotein and its interaction with human CD26. Emerg Microbes Infect. 2020;9(1):601–4.

192. Inn KS, Kim Y, Aigerim A, Park U, Hwang ES, Choi MS, et al. Reduction of soluble dipeptidyl peptidase 4 levels in plasma of patients infected with Middle East respiratory syndrome coronavirus. Virology. 2018 May;518:324–7.

193. Kawasaki T, Chen W, Htwe YM, Tatsumi K, Dudek SM. DPP4 inhibition by sitagliptin attenuates LPS-induced lung injury in mice. Am J Physiol Lung Cell Mol Physiol. 2018 Nov 1;315(5):L834–45.

194. Lim S, Kim KM, Nauck MA. Glucagon-like Peptide-1 Receptor Agonists and Cardiovascular Events: Class Effects versus Individual Patterns. Trends Endocrinol Metab TEM. 2018 Apr;29(4):238–48.

195. Drucker DJ. Mechanisms of Action and Therapeutic Application of Glucagon-like Peptide-1. Cell Metab. 2018 Apr 3;27(4):740–56.

196. Han JH, Oh TJ, Lee G, Maeng HJ, Lee DH, Kim KM, et al. The beneficial effects of empagliflozin, an SGLT2 inhibitor, on atherosclerosis in ApoE -/- mice fed a western diet. Diabetologia. 2017 Feb;60(2):364–76.

197. Hahn K, Ejaz AA, Kanbay M, Lanaspa MA, Johnson RJ. Acute kidney injury from SGLT2 inhibitors: potential mechanisms. Nat Rev Nephrol. 2016 Nov 16;12(12):711–2.

198. Yki-Järvinen H. Thiazolidinediones. N Engl J Med. 2004 Sep 9;351(11):1106–18.

199. Zhang WY, Schwartz EA, Permana PA, Reaven PD. Pioglitazone inhibits the expression of inflammatory cytokines from both monocytes and lymphocytes in patients with impaired glucose tolerance. Arterioscler Thromb Vasc Biol. 2008 Dec;28(12):2312–8.

200. Delea TE, Edelsberg JS, Hagiwara M, Oster G, Phillips LS. Use of thiazolidinediones and risk of heart failure in people with type 2 diabetes: a retrospective cohort study. Diabetes Care. 2003 Nov;26(11):2983–9.

201. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. Intensive Care Med. 2013 Feb;39(2):165–228.

202. Luzi L, Radaelli MG. Influenza and obesity: its odd relationship and the lessons for COVID-19 pandemic. Acta Diabetol. 2020;57(6):759–64.

203. Gombart AF, Pierre A, Maggini S. A Review of Micronutrients and the Immune System-Working in Harmony to Reduce the Risk of Infection. Nutrients. 2020 Jan 16;12(1):236.

204. Gal RL, Cohen NJ, Kruger D, Beck RW, Bergenstal RM, Calhoun P, et al. Diabetes Telehealth Solutions: Improving Self-Management Through Remote Initiation of Continuous Glucose Monitoring. J Endocr Soc. 2020 Sep 1;4(9):bvaa076.

205. Usefulness and Safety of Remote Continuous Glucose Monitoring for a Severe COVID-19 Patient with Diabetes - PubMed [Internet]. [cited 2023 Jan 11]. Available from: https://pubmed.ncbi.nlm.nih.gov/32639844/

206. Lanzola G, Losiouk E, Del Favero S, Facchinetti A, Galderisi A, Quaglini S, et al. Remote Blood Glucose Monitoring in mHealth Scenarios: A Review. Sensors. 2016 Nov 24;16(12):1983.

207. Singh AK, Gupta R, Ghosh A, Misra A. Diabetes in COVID-19: Prevalence, pathophysiology, prognosis and practical considerations. Diabetes Metab Syndr. 2020;14(4):303–10.

208. McGovern AP, Thomas NJ, Vollmer SJ, Hattersley AT, Mateen BA, Dennis JM. The disproportionate excess mortality risk of COVID-19 in younger people with diabetes warrants vaccination prioritisation. Diabetologia. 2021 May;64(5):1184–6.

209. Dispinseri S, Lampasona V, Secchi M, Cara A, Bazzigaluppi E, Negri D, et al. Robust Neutralizing Antibodies to SARS-CoV-2 Develop and Persist in Subjects with Diabetes and COVID-19 Pneumonia. J Clin Endocrinol Metab. 2021 Apr 23;106(5):1472–81.

210. Ali Abdelhamid Y, Kar P, Finnis ME, Phillips LK, Plummer MP, Shaw JE, et al. Stress hyperglycaemia in critically ill patients and the subsequent risk of diabetes: a systematic review and meta-analysis. Crit Care Lond Engl. 2016 Sep 27;20(1):301.

211. Huang C, Huang L, Wang Y, Li X, Ren L, Gu X, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. The Lancet. 2021 Jan 16;397(10270):220–32.

212. Ayoubkhani D, Khunti K, Nafilyan V, Maddox T, Humberstone B, Diamond I, et al. Post-covid syndrome in individuals admitted to hospital with covid-19: retrospective cohort study. BMJ. 2021 Mar 31;372:n693.

213. Zelniker TA, Wiviott SD, Raz I, Im K, Goodrich EL, Furtado RHM, et al. Comparison of the Effects of Glucagon-Like Peptide Receptor Agonists and Sodium-Glucose Cotransporter 2 Inhibitors for Prevention of Major Adverse Cardiovascular and Renal Outcomes in Type 2 Diabetes Mellitus. Circulation. 2019 Apr 23;139(17):2022–31.

214. American Diabetes Association. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes—2020. Diabetes Care. 2019 Dec 16;43(Supplement_1):S14–31.

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.