Dissertation

Glycemic control in type 1 diabetes during COVID-19 pandemic

submitted by

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Declaration

I hereby declare that this thesis is my own original work and that I have fully acknowledged by name all those individuals and organizations that have contributed to the research for this thesis. Due acknowledgement has been made in the text to all other material used. Throughout this thesis and in all related publications I followed the “Standards of Good Scientific Practice and Ombuds Committee at the Medical University of Graz”.

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Disclosures

Parts of this thesis has been published as

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Preface

The analysis of the current thesis was held during the coronavirus disease 2019 (COVID-19) pandemic. Since then, we performed a retrospective data analysis – as physical contact should be minimized in that time. The COVID-19 pandemic had a tremendous global impact in the beginning of 2020. People had no grasp of the major consequences of the virus infection at the time. Ever since, routine hospital appointments were minimized as the fear of an infection was very high in these days. High-risk populations – as people living with diabetes mellitus– were about to be under a special protection of not being infected with the virus.

Even if telemedical care was performed in some countries as it was done in Italy, some people felt – at least in Austria – left alone with their diabetes treatment. This was because most routine appointments were cancelled because of the fear of a possible infection, which also had a high risk to suffer from a severe COVID-19 infection. We wanted to investigate the impact of COVID-19 on diabetes control in people living with type 1 diabetes in Austria.

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Lastly, I want to thank all my colleagues and superiors at the hospital in Wiener Neustadt, for enabling my educational leave and always supporting my project.

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List of abbreviations

ACE	angiotensin-converting enzyme
ACE2	angiotensin-converting enzyme 2
ACS	acute coronary syndrome
ADA	American diabetes association
AID	artificial pancreas or automated insulin delivery
alphaCoV	alphacoronavirus
BAL	bronchoalveolar lavage
betaCoV	betacoronavirus
BG	blood glucose
BMI	body-mass index
CDC	United States Center for Disease Control and Prevention
CGM	continuous glucose monitoring
COVID-19	coronavirus disease 2019
CoVs	coronaviruses
CRP	C-reactive protein
CSII	continuous subcutaneous insulin infusion
CSV data	comma-separated values data
CT	computer tomography
CV	coefficient of variation
deltaCoV	deltacoronavirus
DIC	disseminated intravascular coagulation
DKA	diabetic ketoacidosis
DM	diabetes mellitus
ECDC	European center for disease prevention and control
FDA	Food and Drug Administration
GAD	glutamatedecarbooxylase
gammaVoC	gammacoronavirus
GDM	gestational diabetes mellitus

GI	gastrointestinal
GM-CSF	granulocyte-macrophage colony-stimulating factor
GMI	glucose management indicator
HbA	adult hemoglobin
HbA1c	glycated hemoglobin
HCoV	human coronavirus
HLA-DR/DQ	human leucocyte antigen marker related to DR/DQ domain
IA-2	tyrosine phosphatase-related islet antigen 2
IAA	insulin auto antibodies
ICA	islet cell antibodies
ICU	intensive care unit
IFN-γ	interferon-γ
IL-1	interleukin-1
IL-12	interleukin-12
IL-1β	interleukin-1β
IL-6	interleukin-6
IL-8	interleukin-8
IQR	interquartile range
isCGM	intermittently scanned glucose monitoring
MAGE	mean amplitude of glycemic excursions
MERS-CoV	middle east respiratory syndrome coronavirus
NIH	American national Institute of Health
NPH Insulins	neutral protamin Hagedorn Insulins
NTD	N-terminal domain
OEDG	Austrian diabetes Association
PCR	polymerase chain reaction
RAAS system	renin-angiotensin-aldosterone system
RBD	receptor binding domain
rtCGM	real time glucose monitoring

SARS-CoV	severe acute respiratory syndrome coronavirus
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD	standard deviation
SMBG	self-monitoring blood glucose
T1D	type 1 diabetes
T2D	type 2 diabetes
TAR	time above range
TBR	time below range
TIR	time in range
TLR	toll-like-receptor
TMPRSS2	transmembrane seine protease 2
TNF-α	tumor necrosis factor-α
UK	United Kingdom
USA	United States of America
VOCs	variants of concern
VOIs	variants of interest
vWF	van Willebrand factor
WHO	world health organization
ZnT8	zinc transporters 8
α2β2	α and β chains
+ssRNA	positive-sense single-stranded RNA virus

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Zusammenfassung

Das Ziel der Analyse war die Beurteilung der Diabeteseinstellung vor und während der COVID-19-Pandemie. Daten von Menschen mit Typ 1 Diabetes (T1D), die eine intermittierend gescannte kontinuierliche Glukoseüberwachung (isCGM) mit dem Abbott Freestyle Libre 1-System (Abbott Diabetes Care, Alameda, CA, USA) verwendeten, wurden retrospektiv untersucht. Die Teilnehmer:innenmerkmale wurden aus elektronischen Krankenakten erfasst. Die Daten wurden für drei Zeiträume von jeweils drei Monaten untersucht: Vor dem Lockdown (gleiche Zeit im Vorjahr): 16.03.2019 – 16.06.2019, kurz vor dem Lockdown: 01.12.2019 – 29.02.2019, Lockdown: 16.03.2020 – 16.06.2020. n=64 für die Hauptanalyse, n=80 für die Sensitivitätsanalyse. Es wurden eine Hauptanalyse und eine Sensitivitätsanalyse durchgeführt. Die Hauptanalyse umfasst Teilnehmer:innen mit allen drei Phasen, für die Baseline-Daten verfügbar sind. Die kategorischen Ausgangsmerkmale für die Hauptanalyse waren folgende: 22 Frauen, 42 Männer, 48 auf Pen-basierter Therapie und 16 auf Pumpen-basierter Therapie; die numerischen Ausgangsmerkmale für die Hauptanalyse waren wie folgt: Alter [Jahre]: 33,5 Jahre (Q1-Q3: 26,3; 49,5), Diabetesdauer [Jahre]: 13,5 (Q1-Q3: 5,5; 22,0) Body Mass Index (BMI) [kg/m2]: 24,61 (Q1-Q3: 22,3; 27,0), HbA1c [mmol/mol]: 58,5 (Q1-Q3: 51,0; 69,4), S-Kreatinin [mg/dL]: 0,90 (Q1-Q3: 0,8; 1,0) und FreeStyle Libre-Nutzungsdauer [Monate]: 68,50 (Q1-Q3: 58,0; 79,3). Die Krankenhausbesuche während der bestimmten Phasen waren 0,0 (Q1-Q3: 0,0; 1,0) während des Lockdowns, 1,0 (Q1-Q3: 0,0; 1,0) während des Pre-Lockdowns und 1,0 (Q1-Q3: 0,0; 2,3) während der Zeit vor dem Lockdown (gleiche Zeit im Vorjahr). Die Sensitivitätsanalyse wurde mit gleichem Schema durchgeführt, jedoch wurden hier auch Individuen mit isCGM-Daten aus mindestens 2 Phasen (wobei eine die Lockdown Phase ist) und für welche Baseline-Daten zur Verfügung stehen, inkludiert. Mehrere Glukosebereiche wurden festgelegt wie folgt: <54 mg/dL, 54 - <70 mg/dL, 70 - 180 mg/dL, >180 - 250 mg/dL and >250 mg/dL. Auch die gesamten isCGM-Scanfrequenzen und die mittleren täglichen isCGM-Scanfrequenzen wurden ausgewertet.

Die beste glykämische Kontrolle basierend auf allen analysierten Parametern (sowohl Haupt- als auch Sensitivitätsanalyse) wurde während des ersten österreichweiten Lockdowns im Vergleich zu Zeiträumen vor dem Lockdown erreicht.

Abstract

The aim of our analysis was to assess glycemic control before and during the COVID-19 pandemic. Data of people with type 1 diabetes (T1D) using intermittently scanned continuous glucose monitoring (isCGM) using Abbott Freestyle Libre 1 system (Abbott Diabetes Care, Alameda, CA USA) was investigated retrospectively. Participant characteristics were collected from electronic medical records. Data were examined for three periods of three months each: pre-lockdown (same season): 16.03.2019 – 16.06.2019, pre-lockdown: 01.12.2019 – 29.02.2019, lockdown: 16.03.2020 – 16.06.2020. Data of people living with T1D were investigated; n=64 for the main analysis, n=80 for the sensitivity analysis. Main analysis and sensitivity analysis was performed. The main analysis includes participants, for whom baseline data are available for all the three periods. Categorical baseline characteristics for the main analysis were as follows: 22 females, 42 males, 48 using a pen and 16 using a pump for diabetes management. Data are indicated as median and interquartile range, as appropriate. Baseline characteristics for the main analysis were as follows: age [years]: 33.5 years (Q1-Q3: 26.3; 49.5), diabetes duration [years]: 13,5 (Q1-Q3: 5.5; 22.0); body mass index (BMI) [kg/m2]: 24.6 (Q1-Q3: 22.3; 27.0), HbA1c [mmol/mol]: 58.5 (Q1-Q3: 51.0; 69.3), S-Creatinine[mg/dL]: 0.9 (Q1-Q3: 0.8, 1.0) and FreeStyle Libre use duration [months]: 68.5 (Q1-Q3: 58.0, 79.3). Visits during the certain phases were 0.0 (Q1-Q3: 0.0, 1.0) during lockdown, 1.0 (Q1-Q3: 0.0, 1.0) during pre-lockdown and 1.0 (Q1-Q3: 0.0, 2.3) during pre-lockdown (same season). Sensitivity analysis was performed with the same scheme, but all individuals with isCGM data during least 2 phases of which one had to be lockdown and for whom baseline data are available are included. Glucose ranges were set at <54 mg/dL, 54 - <70 mg/dL, 70 - 180 mg/dL, >180 - 250 mg/dL and >250 mg/dL. Also, total isCGM scan frequencies and mean daily isCGM scan frequencies were evaluated.

Best glycemic control based on all parameters analyzed (for both main and sensitivity analysis) was achieved during the first Austrian-wide lockdown compared to pre-lockdown periods.

1. Introduction

1.1. Pandemic

The Coronavirus disease 2019 (COVID-19) outbreak in 2020 serves as the perfect model for understanding what a pandemic is. To explain why this is the case, a definition of epidemic and endemic is necessary. An epidemic is an unexpected increase in the number of disease cases in a specific geographical area (2). Examples for that are e.g. measles, smallpox, or yellow fever. Also, the west Nile fever or the rapid increase in obesity rates can be an epidemic. They do not have to be contagious and are limited to a community or region but are limited in time. An endemic disease outbreak is consistently present but limited to a particular region, as, for example, malaria is. A pandemic occurs, when e.g. the virus affects several countries and populations and covers a wide area and thus, is an endemic that spreads over borders. Notable pandemics in the past were the Black Death (1346-1453), the Flu pandemic (1889-1890), the Spanish Flu (1918-1920) or the Asian Flu (1957-1958) as well as the latest COVID-19 pandemic. The field of epidemiology deals with tracing the sources with the goal to ensure public health (3).

1.1.1. Sars-CoV-2 or COVID-19 pandemic

COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and is a highly contagious and infectious disease raised from the subfamily *Orthocoronaviridae* or the *Coronaviridae* family. With more than 6 million deaths worldwide, COVID-19 has emerged as the most consequential global health crisis since 1918's pandemic of influenza (4). Accordingly, screening, identification, treatment recommendations and prevention strategies have been developed in a very short time. SARS-CoV-2 disseminated worldwide, after first cases were reported in Wuhan, Hubei Province, China, in late December 2019. On March 11th in 2020 the WHO declared it a global pandemic (5). As a positive-sense single-stranded RNA virus (+ssRNA), SARS-CoV-2 adapts with genetic evolutions which caused to several variants of SARS-CoV-2. Spike glycoproteins are on the envelops and investigations under the electron microscope show crown-like appearance beneath (5).

The world health organization (WHO) has classified variants of concern (VOCs) and variants of interest (VOIs) to distinguish due to their potential. Since the beginning of the pandemic 5 SARS-CoV-2 VOCs have been identified: Alpha (B1.1.7) - United Kingdom (UK) in December 2020 (2); Beta (B.1.351) – South Africa in December 2020 (2), Delta (B.1.617.2) – India in

December 2020 (2), Gamma (P.1) – Brazil in January 2021 (2), Omicron (B.1.1.529) – South Africa in November 2021 (6).

1.1.1.1. Etiology

The *Orthocoronaviridae* of the *Coronaviridae* family classified Coronaviruses (CoVs) into four genera: Alphacoronavirus (alphaCoV), Betacoronavirus (betaCoV) – which is further divided into five sub-genera or lineages, Deltacoronavirus (deltaCoV) and Gammacoronavirus (gammaCoV). AlphaCoVs and betaCoVs seem to have their gene sources in bats and rodents while deltaCoVs and gammaCoVs probably have their genomic characterization from avian species (7).

Seven human CoVs (HCoVs) are identified so far. This enables the virus to affect humans as well by crossing species barriers. Common HCoVs that can cause common respiratory tract infections and colds are HCoV-NL63, HCoV-OC43, HCoV-HKU1 and HCoV-229E. Other human CoVs which can unfortunately also cause severe respiratory and extra-respiratory infections by being more virulent are SARS-CoV and MERS-CoV (Middle East Respiratory Syndrome Covonavirus) (5). The novel BetaCoV SARS-CoV-2 can be attributes to the same subgenus as the SARS-CoV and MERS-CoV (8). Genomic analysis suggest that SARS-CoV-2 has zoonotic transmission and origins from a strain found in bats (4,9).

Transmission of SARS-CoV-2 mainly occurs via exposure to respiratory droplets carrying the infectious virus. Also, airborne transmission with aerosols and fomite transmission from contamination of inanimate surface has been described (5). Data reports that individuals with SARS-CoV-2 infection have living viruses in their feces, which does not exclude a fecal-oral transmission (10). Vertical transmission from infected mothers to neonates is possible but rare (11).

1.1.1.2. Epidemiology

The United States Center for Disease Control and Prevention (CDC) gained data from February 2020 to July 2022 and states that the infection can be contracted by individuals of all ages, but patients aged ≥60 years are at a higher risk of death. Persons aged 50 to 64 years have a 25-times higher risk of death when being infected with COVID-19 compared to adults younger than 30 years old. This risk increases to 60 times in persons aged 65 to 74 years and 340 times in patients older than 85 years. The data includes all deaths in the United States throughout the pandemic (unvaccinated individuals included) (12).

Furthermore, patients with relevant comorbidities have an increased risk of suffering from severe COVID-19 infections. Main risk-factor comorbidities are cancer, cardiovascular disease, chronic lung disease and chronic kidney disease. Obesity and smoking also increases the risk. Solid organ or hematopoietic stem cell transplant patients are endangered. Data from January 22 to May 30 2020 reports that patients with a preexisting medical condition have a 6 times higher risk of hospitalization (45.4%) than individuals without any medical condition (7.6%) (13).

Male patients have a higher risk of severe illness and increased mortality when being infected with COVID-19 compared to females. This gender-based data comes from a retrospective cohort study from acute care hospitals in the United States of America (USA) from March 2020 to November 2021. The outcomes indicate a mortality rate of male patients of 12.5% and compared to a rate of 9.6% in females and included 42,604 patients with confirmed SARS-CoV-2 infections (14–16).

1.1.1.3. Pathophysiology

The phylogenetic and structure of SARS-CoV-2 is very similar to SARS-CoV and MERS-CoV. It contains 16 nonstructural proteins, 5-8 accessory proteins and the four main structural proteins envelope (E), membrane (M), nucleoside (N) and spike (S) (17,18).

The surface spike (S) glycoprotein is located on the surface of the virion – it is similar to a crown. The virus can incorporate into the host cell by cleaving into an amino (N)-terminal S1 subunit. This S1 subunit is further divided into an N-terminal domain (NTD) and a receptor-binding domain (RBD) – this RBD domain is a fundamental peptide in the pathogenesis of infection. It is a binding site for the human angiotensin-converting enzyme 2 (ACE2) receptor. The NTD enables viral entry into the host cell. This NTD is a potential target for neutralization and thus, is an important part in developing antisera or vaccines.

The other domain, a cytoplasmic domain, a fusion peptide, and a transmembrane domain make the carboxyl (C)-terminal S2 unit. The cytoplasmic domain is responsible for virus-cell membrane fusion (19).

SARS-CoV-2 spike protein (S1) binds to the ACE2 receptors in human's respiratory epithelium. ACE2 receptors are further expressed by enterocytes from the ileum, the esophagus, myocardial cells, and cells from the kidneys, urothelium and bladder. The host transmembrane serine protease 2 (TMPRSS2) is attached by the spike protein 2 (S2). Viral replication, that causes tissue damage, is the result (20,21). This happens in the early phase of infection, while T-lymphocytes, monocytes and neutrophils are recruited in the late phase. In the further phase,

a local and systemic inflammatory response takes place by releasing interleukin-1 (IL-1), interleukin-1β (IL-1β), interleukin-6 (IL6), interleukin-8 (IL-8), interleukin-12 (IL-12), tumor necrosis factor-α (TNF-α), interferon (IFN)-γ and granulocyte-macrophage colony-stimulating factor (GM-CSF) (22).

SARS-CoV-2 affects the **respiratory system**, which is the principal target, as well as the **extrapulmonary organ system**. Lung inflammation (up to lung fibrosis) is the result of the binding of SARS-CoV-2 to the toll-like-receptor (TLR) whereby IL-1β is released. Disturbance of intercellular junctions is the result of enhanced epithelial cell contraction and the thereby accrued swelling. Renin-angiotensin-aldosterone system (RAAS) are dysregulated due to increased binding of the virus to the ACE2 receptors and vascular permeability and gets enhanced by activation of the kallikrein-bradykinin pathway. Furthermore – as a result of direct viral injury and perivascular inflammation – endotheliitis leads to microvascular impairment and microthrombi deposition (23).

SARS-CoV-2 induced organ function can also affect the cardiovascular system, central nervous system, gastrointestinal (GI) tract as well as the hepatobiliary and renal system. Those dysfunctions mostly occur by a combination of direct viral toxicity, immune dysregulation, ischemic injuries caused by vasculitis, RAAS dysregulation and thrombosis.

Pro-inflammatory cytokines like IL-6 can lead to cardiac arrhythmias, myocarditis and vascular inflammation by ACE2 receptor exhibition. Moreover, acute coronary syndrome (ACS) can occur since reduced coronary blood flow, micro thrombogenesis, coronary plaque destabilization and exhibition of pro-inflammatory cytokines are common side effects of the infection (24,25)

Hematological and hemostatic systems can be affected as well. Thrombocytopenia is a marker for severe illness caused by virus-mediated suppression of platelets and coagulation cascade activation. The vascular endothelium is viral-mediated or cytokine-induced damage that leads to activation of macrophages, monocytes, and platelets with increased expression of Factor VIII and von Willebrand factor (vWV) resulting in thrombin and fibrin clots generation. Leukopenia and the reason why it mostly occurs in cases of severe COVID-19 infections is widely unknown. Interactions with the ACE2 receptor are under estimation, but this is not clear yet (26–28).

1.1.1.4. Manifestation

COVID-19 infection may begin asymptomatically. This is estimated for 17.9% -33.3% of affected people with a median incubation period of 5.1 days and a symptom development

within 11.5 days after infection (29). In that case, patients are dangerous spreaders of the virus as they commonly do not reduce contact to others and thus pass the virus on to their environment. However, most people have mild symptoms like cough, including sore throat, fever, GI manifestation with diarrhea, headache or anorexia. Only a few suffer from severe symptoms which mostly include acute respiratory failure that requires mechanic ventilation or septic shock up to multi-organ failure (30,31).

A meta-analysis of 212 published studies including more than 280,000 individuals from eleven countries reported a mortality rate of 6% and a severe disease course in about 23% of COVID-19 infected (30). Another meta-analysis including about 8,600 Chinese patients reported laboratory abnormalities including elevated C-reactive protein levels (65.9%), elevated cardiac enzymes (49.4%), lymphopenia (47.6%), abnormal liver function tests (26.4%), leukopenia (23.5%), elevated D-dimer and elevated erythrocyte sedimentation rate (both with 20.4%), elevated procalcitonin (16.7%), abnormal renal function tests (10.9%) and leukocytosis (9.9%) (30,31).

National and international institutes have determined guidelines to classify COVID-19. WHO as well as the European center for disease prevention and control (ECDC) or the American National Institute of Health (NIH) have released guidelines to classify COVID-19 into distinct types, based on their severity (32,33).

1.1.1.5. Evaluation

Oropharyngeal swabs, anterior/mid-turbinate nasal swabs, nasopharyngeal aspirates, bronchoalveolar lavage (BAL) and most used nasopharyngeal swabs have been authorized for qualitative detection of SARS-CoV-2 by the USA Food and Drug Administration (FDA) and the European Commission for Health and Food Safety.

SARS-CoV-2 antigen testing is less sensitive than molecular polymerase chain-reaction (PCR) testing, as it detects the antigen of the virus. Sensitivity of PCR tests, where the virus-genome is detected, depends on several factors like specimen source and adequacy. The turnaround time of SARS-CoV-2 antigen tests is therefore lower, and results are present several minutes after test performance. PCR testing takes more time in evaluation even if there are plenty of fast-track tests available already (34).

Serological testing is limited in specificity and sensitivity and thus not recommended as a state-of-the-art method to detect an infection. However, it can be used to gain information about the antibody status in patients' blood.

Inflammatory markers such as CRP, ferritin, procalcitonin and IL-6 should be checked in all hospitalized patients with a COVID-19 diagnosis connected with upcoming symptoms. Furthermore, renal and liver function testing should be performed, as well as coagulation tests including a D-dimer test (34,35).

A chest x-ray that usually shows bilateral multifocal alveolar opacities and pleural effusion supported by a chest computed tomography (CT), mostly showing multifocal bilateral ground glass opacities with consolidation changes in a patchy peripheral distribution are common imaging methods in symptomatic patients. Lung ultrasound may be conducted as well, even if there are no guidelines for imaging modalities in detecting COVID-19 disease (35).

1.1.1.6. Treatment / Management

According to the ECDC and the NIH most SARS-CoV-2 infections can be managed at home without hospitalization. Treatment is mostly supportive oxygen or ventilation for critical patients.

As the pathogenesis of COVID-19 can be categorized into two main steps, there are two possibilities of treatment approach – besides supportive oxygen treatment, if needed. Firstly, to stop virus replication, antiviral medication is indicated. Secondly, the illness and dysregulated immune/inflammatory response leading to systemic tissue damage requires immune modulators. Systemic corticosteroids and IL-6 receptor-blockers (tocilizumab or baricitinib) can be used. WHO strongly discommends antimalarial hydroxychloroquine and antiretroviral lopinavir-ritonavir for COVID-19 treatment and also recommend against the antiparasitic ivermectin, except in the context of clinical trials. Severe disease can be treated with convalescent plasma. (36).

1.1.1.6.1. Medicines

For non-hospitalized patients, there are several products authorized besides the use of oxygen. For people that are at a high risk to develop severe disease, an oral antiviral nirmatrelvir and the protease inhibitor ritonavir can be used as well as antiviral monoclonal antibodies, such as sotrovimab or a combination of the two monoclonal antibodies tixagevimab and cilgavimab, or casirivimab and imdevimab. For hospitalized patients who need oxygen, remdesivir can be used as an antiviral treatment. Also, immune modulators such as tocilizumab, anakinra or baricitinib can be used. These options are based on adult treatment experience; data for treatment in children is still limited (37).

1.1.1.6.2. Vaccination

Bimervax, developed by HIPRA Human Health S.L.U., Comirnaty from BioNTech Manufacturing GmbH of BioNTech and Pfitzer, COVID-19 Vaccine Valneva, from Valneva Austrian GmbH, Jcovden, developed by Janssen-Cilag International NV, Nuvaxovid from Novavax CZ, a.s., Spikevax developed by Moderna Biotech Spain (S.L.), Vaxzevria from AstraZeneca AB and VidPrevtyn Beta developed by Sanofi Pasteur are vaccines used within the EU (37).

1.1.1.7. Differential Diagnosis

As symptoms are nonspecific, a broad range of differential diagnosis such as influenza infection, bacterial or viral pneumonia, aspiration pneumonia, MERS or pulmonary tuberculosis must be excluded. This is especially based on the very nonspecific symptoms which SARS-CoV-2 has in the early stage of infection (4).

1.1.1.8. Prognosis

The global case fatality rate estimated by the WHO for COVID-19 is 2.2%. A French cohort study with 4000 critically ill patients from France, Belgium and Switzerland with COVID-19 admitted to an intensive-care unit (ICU) reported a 90-day mortality of 31%. Mortality is higher in older, obese and diabetic patients (38).

The prognosis on outcomes of COVID-19 infections depends on various factors such as age, preexisting conditions, and severity of illness. How quickly treatment starts and how good the response to the treatment is are other important factors (39).

1.1.1.9. Complications

COVID-19 complications are various, as the virus causes illness which involves multiple organ systems. The most common complication is acute respiratory failure or multi-organ failure that leads to death. Studies have shown that other severe COVID-19 associated complications occur mostly in elderly persons that mostly have additional comorbid conditions such as cancer, cardiovascular disease, chronic liver- lung- or kidney disease, diabetes mellitus or obesity. Patients affected by the virus are furthermore often affected by gastrointestinal complications such as gastrointestinal bleeding, mesenteric ischemia, pancreatitis and severe ileus (40). They are also at a higher risk of developing arterial thrombosis, ischemic strokes,

myocardial infarctions (or other cardiomyopathies up to cardiogenic shock) and pulmonary embolism. Acute renal failure is the extrapulmonary manifestation that is most common in COVID-19 patients. All those are associated with an increased mortality risk (27) (27).

Most patients affected by a severe COVID-19 infection suffer from invasive fungal infections such as aspergillosis and mucormycosis, which is more likely when other comorbid conditions such as associated lymphopenia, the use of corticosteroids or an uncontrolled diabetes exist.

Plenty of retrospective studies are available yet concerning different fields of clinical important effects. Psychiatric and neurological effects are assured in a retrospective cohort study including more than 230,000 patients. They reported anxiety and psychiatric disorders as well as intracranial hemorrhage and ischemic stroke six months after being diagnosed with COVID-19. From another cohort study emerged a post-acute COVID-19 syndrome in patients who recovered from COVID-19. Most of them developed symptoms such as anxiety, fatigue, muscle weakness or sleep difficulties. This study was performed six months after hospitalization (41). Another meta-analysis study determined the association of disseminated intravascular coagulation (DIC) with COVID-19 infection and detected a severe illness and poor prognosis for these patients when monitoring of coagulation indicators was poor (42).

Nearly all studies claim diabetes as an increased risk factor for suffering from severe COVID-19 disease when being affected. Thus, good glucose control must be ensured – which is associated with a close-meshed treatment. Since many of those routine appointments were neglected during the pandemic in 2020 our research question arises.

1.1.1.9.1. Covid-19 and type 1 diabetes

As diabetes mellitus (DM) affects 1 out of every 11 people worldwide and it was the ninth leading cause of death in 2019, we wanted to have a closer look regarding the effects of COVID-19 on people living with diabetes, specifically in people living with type 1 diabetes (43). Even if - with continuous glucose monitoring (CGM) - hyper- and hypoglycemia can be reduced and diabetes can be better managed nowadays, proper diabetes management also requires close routine medical appointments, medical support and insulin dose adjustments as well assessment and treatment of comorbidities. Many routine physician appointments were skipped due to fear of infection with COVID-19, insufficient human resources in the outpatient clinics or the concentration of care for acutely or severely ill patients. As a consequence of that, diabetes control has deteriorated during this period with increased times below and above ranges (44–46). Data also suggest that people with poor glycemic control suffer from more

severe Coronavirus disease and are at higher risk of death (47,48). Thus, it is essential to achieve good glycemic control even when access to physicians for routine care is limited.

Furthermore, biopsychosocial factors such as stress can negatively affect glycemic control in diabetes. The missing clinical support of medical staff during COVID-19 could be further stressful for the people living with diabetes. Therefore, we wanted to investigate the impact of COVID-19 on diabetes control in people living with type 1 diabetes in Austria.

1.2. Diabetes

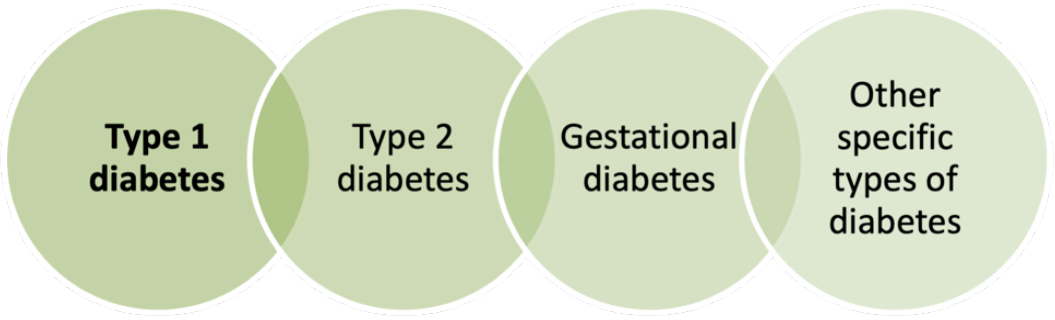

Figure 1 – The four types of diabetes

Diabetes can be classified in four types. Type 1 diabetes (T1D), type 2 diabetes (T2D), gestational diabetes mellitus (GDM) and specific types of diabetes due to other causes, as presented in Figure 1. **T1D**, is caused by an autoimmune β-cell destruction which commonly leads to absolute insulin deficiency, including latent autoimmune diabetes of adulthood. **T2D** is characterized by insulin resistance combined with progressive loss of adequate β-cell insulin secretion.

There are several criteria that enable to distinguish between T1D and T2D according to the Austrian Diabetes Association (OEDG). Table 1 gives an overview on the main criteria (49,50).

Criteria	T1D	T2D
Frequency	Rare (<10%)	Frequent (>90%)
Body weight	Mostly normal weight	Mostly overweight
Age of manifestation	Mostly at young age	Mostly at higher age

Symptoms	Frequent	Rare
Familial accumulation	Rare	Frequent
Insulin therapy	Instantly needed	Mostly after long progress; firstly lifestyle modification and non-insulin medication
HLA-Association	+ (HLA-DR/DQ)	-
Diabetes-associated antibodies	85-95% + (GAD, ICA, IA-2, IAA, ZnT8)	-
Plasma-C-peptide	Mostly low or not present	Mostly normal or increased, over time reduced
Diabetic Ketoacidosis (DKA)	Characteristically, often at diagnosis	Very rare

Table 1 – Criteria for classification of T1D and T2D according to the guidelines of the OEDG (adjusted from 49)

GDM usually develops during the second or third trimester of gestation and is mostly caused by intermittent insulin resistance, in some cases as first manifestation of T1D or T2D. Other **specific types of diabetes**, can be drug- or chemically-induced diabetes e.g. caused by glucocorticoid use in **HIV/AIDS** treatment or after organ transplantation, or diseases of the exocrine pancreas, such as pancreatitis or cystic fibrosis or monogenic diabetes syndromes (51). While having different origins, all types of diabetes have the same features of pathology: elevated glucose levels. Currently used methods to achieve normoglycemia will be dealt with in the following section. This thesis focuses on type 1 diabetes as all individuals that were part of the current investigation were previously diagnosed with this condition.

1.2.1. Diagnosis

According to the OEDG, Figure 2 gives an overview on commonly used standard methods to diagnose diabetes mellitus (DM) as well as an increased risk or prediabetes(49).

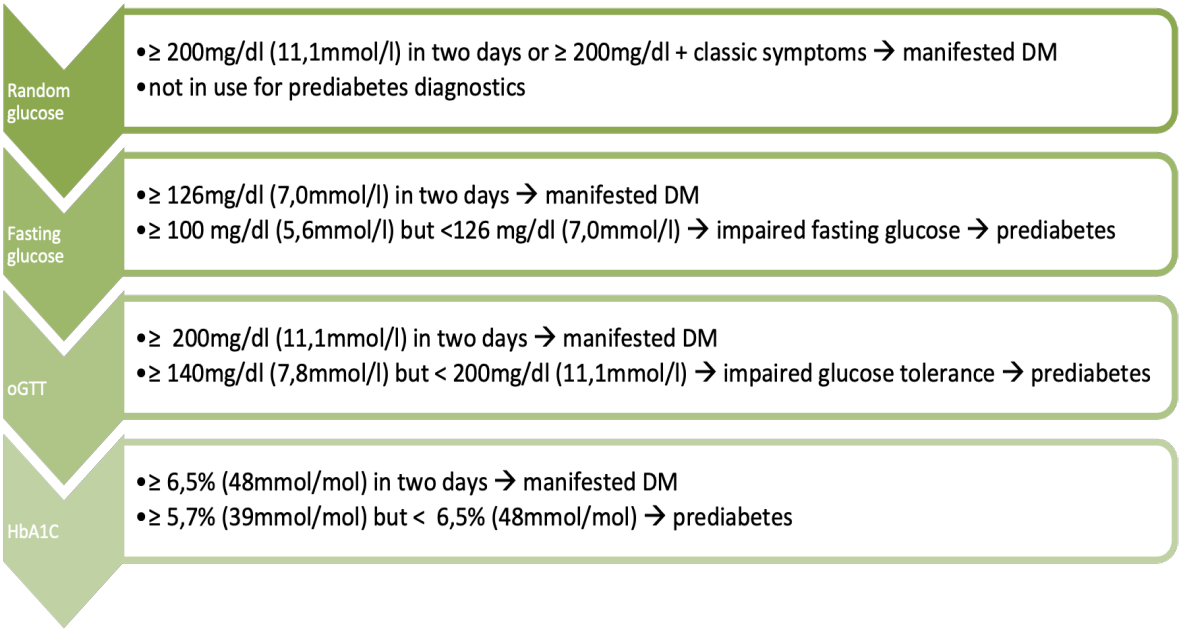

Figure 2 – Overview of the four common steps of diabetes diagnostics according to the OEDG guidelines (adjusted from 49)

Random glucose can be measured either venous or capillary. It can give a first hint to a present manifestation of diabetes. Fastening glucose should usually be <100mg/dL in venous plasma. An oral glucose tolerance test is performed 2 hours after taking 75g of glucose and measures blood glucose level from venous plasma. HbA1c can be normal at initial manifestation of T1D. All tests must be proven by double confirmation, except if classical clinical symptoms are present. Metabolic derailment up to a diabetic ketoacidosis mostly results in symptoms such as polyuria, polydipsia, impaired vision, weight loss and an increased infection tendency with it (49).

1.2.2. Monitoring

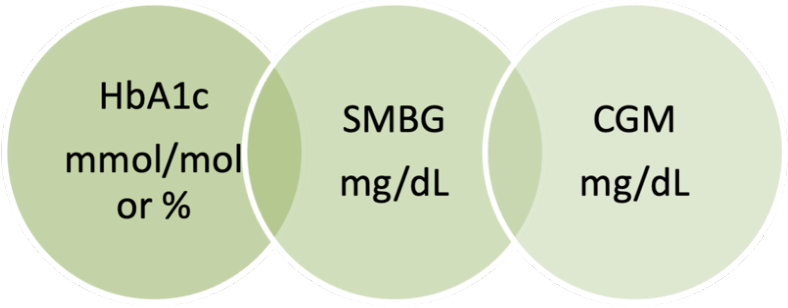

Figure 3 – Methods to assess glycemic control

Figure 3 gives an overview in the commonly used system measuring glucose in people living with T1D. Over the years, several parameters have been established in monitoring people living with diabetes. Those parameters did not fundamentally change within the years, however, are still of high importance. The commonly used parameters such as **HbA1c** and **BG** are the same parameters of interest in people living with type 1 diabetes and type 2 diabetes. Also in healthy adults, children, or pregnant women HbA1c and blood glucose is commonly used for diabetes diagnosis and follow-up. Blood glucose measured either by self-monitoring of blood glucose (SMBG) or via blood taking at a laboratory setting gives information about the currently given glucose level.

CGM just came up in the last two decades. It measures interstitial glucose via a glucose sensor, approximately every five minutes. With that, closely measured glucose monitoring received a new definition.

It aids with distinguish between initial (while diagnosing) diabetes monitoring and follow-up monitoring. While the metric device HbA1c is a parameter of use by doctors and medical stuff, SMBG and CGM is used from patients themselves to check glycemic status (52).

1.2.2.1. HbA1c

The iron-containing oxygen-transport protein in erythrocytes in named hemoglobin. Normal adult hemoglobin (HbA) has a hem moiety and two globin chains (α and β chains (α2β2)) that make up to 97% of adult hemoglobin. Within HbA approximately 6% is glycated, with the minor components HbA1a and HbA1b (1%) and the main component HbA1c (5%) (53). Via the non-enzymatic process of glycation, HbA1c results from the covalent attachment of glucose to the N-terminal valine of the hemoglobin β-chain (54).

Thus, this marker is dependent on the interaction between the lifespan of the erythrocytes and the concentration of blood glucose. HbA1c reflects average glucose over the last 8-12 weeks, as the mean erythrocyte lifespan is approximately 120 days, and still is the key surrogate marker for developing long-term diabetes complications in people living with type 1 or type 2 diabetes. Recommended by the American Diabetes Association (ADA), the glycated hemoglobin HbA1c is the standard of assessing glycemic control in people living with diabetes since 1988 (55). Initially not being endorsed for establishing the diagnosis of diabetes, HbA1c has in the meantime been validated by the ADA in 2010 as a diagnostic criterion for diabetes. People at high risk to develop diabetes should have their HbA1c measured once a year while people living with diabetes should be tested up to four times per year. The cutoffs are set at ≥ 48 mmol/mol (≥6.5%), prediabetes of ≥39mmol/mol (≥5.7%) and normal at <39mmol/mol

(<5.7%). HbA1c ≥48 mmol/mol (≥6.5%) measured by a validated method is diagnostic for diabetes (51). Usually, HbA1c is measured in mmol/mol, sometimes also % values can be found. HbA1c in percent = (0.09148*HbA1c in mmol/mol) + 2.152. That means a HbA1c of 6.5% is the same than a HbA1c of 48mmol/mol (50). As each laboratory parameter has limitations, also HbA1c measurement may be limited by various conditions as listed in Table 2 (55,56).

1.2.2.1.1. Causes of false high or false low HbA1c

Causes of false HbA1c		
Mechanism	**False high HbA1c**	**False low HbA1c**
Altered hemoglobin	– Hemoglobin variants – Hemoglobinopathies	
Assay-related artifacts	– Aspirin-induced acetylated hemoglobin – Cigarette-associated carboxyhemoglobin – Hyperbilirubinemia – Hypertriglyceridemia – Uremia	
Change in glycation	– Blood transfusion	– Vitamin E
Change in red blood cell lifespan or turnover	– Asplenia – Folate deficiency – Iron deficiency – Vitamin B12 deficiency	– Acute or chronic blood loss – Blood transfusion – Cystic fibrosis – related diabetes – Hemolytic anemia – Hypersplenism – Iron/erythropoietin-stimulating agent administration

	– Pregnancy – Renal failure – Spherocytosis

Table 2 – Causes for false high or false low HbA1c measurements (adjusted from 56–58,58)

In conclusion, causes of false high or false low HbA1c measurements can be assay-related artefacts, changes in glycation and hemoglobin or factors concerning the lifespan or turnover of the erythrocytes.

The most limiting factor of HbA1c is the lack of information about the acute glycemic status and complications of hypo- and hyperglycemia as it does not account for day-to-day glycemic variability (39,55,56). No statement about the magnitude and frequency of intra- and inter-day glucose variation can be made on the base of HbA1c. Even if glucose levels of individuals with diabetes differ widely, they may have the same HbA1c as Figure 4 shows.

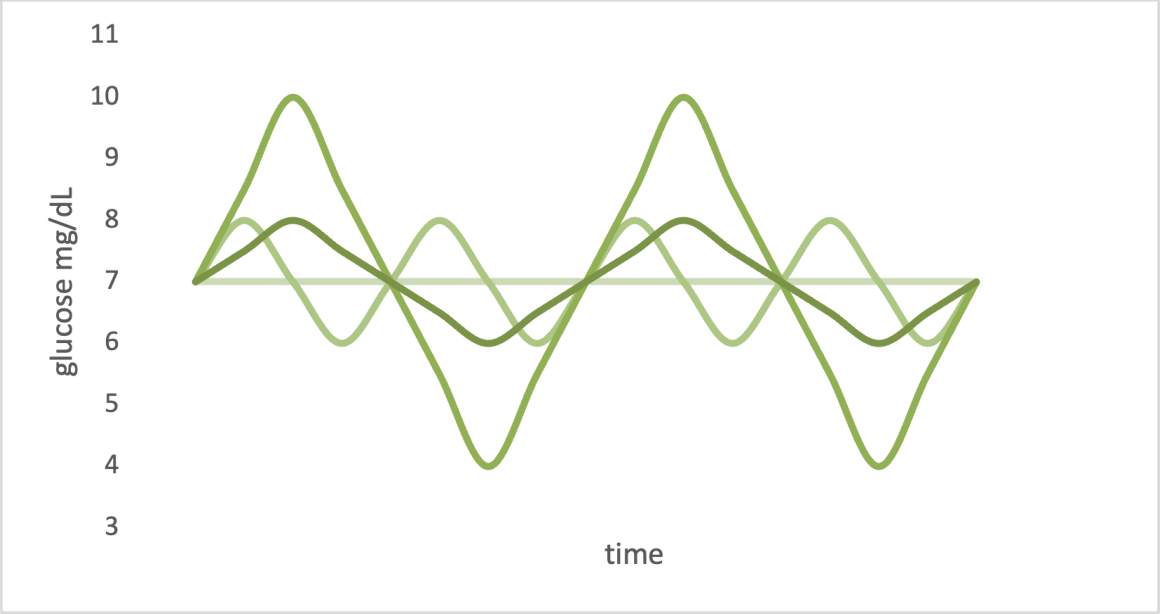

Figure 4 – Three glucose profiles with different degrees of glucose variability and the same mean blood glucose

Circumstances as listed in Table 2 can confound HbA1c measurements additionally, and they sometimes fail to accurately reflect mean glucose.

However, HbA1c still is the gold standard method in long term evaluation of diabetes control for clinical staff and should not be undervalued. When using it in combination with glycemic data measured by CGM, its utility is highly enhanced. To obtain detailed information of glycemic patterns and daily profiles, the use of CGM is highly recommended (52) to enable useful treatment adjustments.

1.2.2.2. Blood glucose (BG) and self-monitoring of blood glucose (SMBG)

Glucose is a 6-carbon structure which is a ubiquitous source of energy for every organism. Bodies can metabolize glucose as monosaccharides (galactose and fructose), disaccharides (lactose and sucrose) or polysaccharides (starch) and can store excess glucose as glycogen. Glycogen becomes liberated in times of fasting. Determination of BG can be performed capillary by finger stick or venous blood draw. Venous blood draw is performed within clinical check-ups, while finger-stick measurements can be easily performed by people living with diabetes themselves. Glucose as a laboratory parameter is a low-price but highly important parameter that is used for over 50 years. Normal blood glucose (BG) between 60 und 140 mg/dL is physiologically regulated in healthy individuals. In case of **hypoglycemia** the need for action is acute, as it can lead to delirium or death (49)(59). Of course, postprandial glucose levels can be higher for about two hours, but the average should be found in range.

1.2.2.3. Continuous Glucose Monitoring (CGM)

Unlike HbA1c, but similar to SMBG, CGM offers comprehensive information on glucose variability and trends. CGM offers an automated glucose monitoring that is done by measuring intestinal glucose via sensors, which happens every 1-15 minutes. Diabetes management can thereby be individualized by clinicians on basis of the continuous data of diabetes pattern (60).

The goal is, to achieve a time in range (TIR) between 70 mg/dL and 180 mg/dL ($TIR_{70\text{-}180mg/dl}$) for more than 70% of glucose values per time, e.g. 24 hours or 2 months, which equalizes an HbA1c 53mmol/mol. Time above range (TAR) should be <25% ($TAR_{>180mg/dl}$) and time below range (TBR) should be <5% ($TBR_{<70mg/dl}$) – whereby < 4% should be <70mg/dL and <1% <54mg/dL - with CGM (49).

1.2.2.3.1. Real time CGM (rtCGM) and intermittently scanned CGM (isCGM)

Real-time CGM (rtCGM) and intermittently scanned CGM (isCGM) – which both are adaptions of CGM – has grown rapidly in the last several years. While rtCGM continuously shows values and courses on a smart phone app or monitoring device with an alarm function when overriding or falling below a pre-defined cutoff, isCGM shows values and trends just when scanning the sensor with a certain reader or a smartphone – also in isCGM there are alarm functions available (49).

Many studies have demonstrated significant clinical benefits of CGM use which may be a result of improvements in great convenience, sensor accuracy and simplicity in use. Continuous expanding of reimbursement is also bringing CGM closer to diabetes patients. Even if clinical use increased highly in the last several years, successful use of CGM in clinical routine is still too low. Reasons for that could be that there is still a lack of clear glycemic targets that people living with diabetes and medical staff can work towards together (39).

1.2.2.3.1.1. isCGM of Abbott FreeStyle Libre

The FreeStyle Libre (Abbott Diabetes Care, Alameda, CA USA) (61) glucose monitoring system includes a sensor that is applied on the back of the upper arm. It continuously measures glucose and can be kept there for up to 14 days. It is paired with a reader or a smartphone app where glucose levels can be read. It shows the current time, the actual level of battery, the number of days the sensor can be used, the current BG level in mg/dL and the trend of the BG. Furthermore, it shows a diagram of BG on the y-axis and time on the x-axis which enables to track glucose levels over multiple days. Time in targets for certain days can be shown as well as low glucose events for a certain period. With the FreeStyle the whole system can also be connected to a smartphone where the proper application hast been downloaded. Another useful tool is the FreeStyle Libre LinkUp App. Glucose levels and trends as well as glucose history can be shown to people who have downloaded the app on their smartphone. This is especially helpful for children and elderly people with T1D as this alarm can go to e.g. a parent's phone (61).

The FreeStyle Libre system is currently used by about 4 million people across 60 countries worldwide and is already available in its 3rd generation. As reimbursement is given for most people using the FreeStyle Libre system living with T1D, it is a new state of the art method in glucose monitoring and improves glycemic control of people living with diabetes (61).

A meta-analysis of real-world observational studies confirmed the reduction in HbA1c in association with the FreeStyle Libre system. The authors identified 75 studies reporting data of approximately 30,000 participants living with diabetes using the FreeStyle Libre system using a random effects model. They investigated that a higher HbA1c at the start of CGM is correlated with greater reduction in HbA1c – thus, the reduction is greater in people with higher baseline HbA1c, sustained for 24 months in patients living with type 1 diabetes (58).

As gained data could also be read by health care teams, diabetes monitoring improved, goals of glucose time in range and HbA1c reduction could be achieved. Accordingly, the therapy of diabetes could be brought to a new level which results in new and better conditions for improving diabetes care. As the COVID-19 pandemic arrived in 2020, this was of high importance to ensure good settings for people living with diabetes.

Of course, there are also several issues that subsequently arose, which must be investigated in closer detail in the next years. One of those questions is whether the pandemic had a high impact on the blood glucose levels of people living with T1D – which is dealt with in the current thesis (62).

1.2.3. Therapy

The increase in blood sugar in combination with DM is a decisive factor in the development of micro-and macrovascular complications and diseases. For this reason, therapy for DM aims to achieve good glycemic control and thereby avoid acute and subsequent complications, achieve reductions of symptoms and thus, restore or maintain quality of life (63,64). For people with T1D, insulin therapy is a vital hormone replacement therapy.

1.2.3.1. Insulins

Insulins can be divided three groups of which the most important insulin types are short-acting and long-acting human insulins or insulin analogues. Additionally, pre-mixed insulins still exist. Short-acting insulins and short-acting insulin analogues can be routinely administered subcutaneously using insulin pens, insulin pumps or rarely using insulin syringes. In the hospital setting, these short-acting insulins can also be administered intravenously. This is specifically relevant cases of metabolic imbalance, e.g. patients in intensive care with parenteral nutrition, insulins can be given via venous administration (49). Long-acting insulins and premixed insulins can only be administered subcutaneously using insulin pens or syringes.

Adverse effects of insulin therapy in general are hypoglycemia and weight gain. Rarely, electrolyte imbalances such as hypokalemia can also occur (especially when administered intravenously) (65).

Regular insulin is a form of insulin that is used prandially and as correction insulin and is characterized by an onset of action after about 30 minutes after injection. It's maximal effect is at about 1.5-3.5 hours after injection and it has a maximum duration of action up to 8 hours (64).

Short-acting insulin analogues such as insulins aspart, glulisine or lispro are characterized by an onset of action after about 5-15 minutes, a maximum effect of 1-3 hours and a duration of action of 3-5 hours after injection. They are used as bolus insulins. Due to their fast onset of action and the shorter duration of action (compared to human insulin), short-acting insulin analogues contribute to improving the quality of life in people living with diabetes mellitus by enabling a shorter injection-eating interval. Studies have also shown, that the rate of hypoglycemia is lower with short-acting insulin analogues (64,66,67).

Moreover, there have recently been ultra-short-acting insulin analogues (FIASP®, Lyumjev®), which ensure a faster circular flow by modifying existing short-acting insulin analogues. Thereby, a faster onset of insulin action and consequently a comparatively better control of postprandial glucose values occurs and enable even shorter injection-eating intervals (64,68–70).

Basal insulins, also named neutral protamin Hagedorn (NPH) Insulin is characterized by its onset of action of 30-60 minutes, a maximum effect of 4-6 hours and a duration of action of 8-14 hours. This is used as basal insulin as part of diabetes therapy. A combination of NPH insulin and regular insulin is called mixed insulin and is primarily used in the treatment of type 2 diabetes (T2D) (55,63,64). Long-acting insulins (insulin glargin U 100, insulin detemir) and ultra-long-acting (insulin glargin U 300 and insulin degludec) insulin analogues are characterized by an onset of action of 30-60 minutes, a flat action curve and a duration of action up to 24 or a maximum of 42 hours. These are also used as basal insulins and show a reduction in nocturnal hypoglycemia in particular compared to NPH insulin (64,71).

Table 3 gives an overview on the main insulins that are commonly in use. Insulin therapy must be immediately started when T1D is diagnosed (72).

Insulins	Sanofi	Eli Lilly	Novo Nordisk
Short-acting insulins	Insuman® Rapid	Huminsulin® Normal	Actrapid®
Short-acting insulin analogs	Glulisin (Apidra®)	Lispro (Humalog®)	Aspart (NovoRapid®)
Ultra short-acting insulin analogs	-	Lispro aabc (Lyumjev®)	Fast-acting Aspart (Fiasp®)
Long-acting insulins	-	Huminsulin® Basal	Insulatard®
Long-acting insulin analogs	Glargin U100 (Lantus®)	-	Detemir (Levemir®)
Ultra long-acting insulin analogs	Glargin U300 (Toujeo®)	-	Degludec (Tresiba®)
Premixed insulins (NPH insulin plus 15-30% regular insulin)	Insuman® Comb 25 Insuman® Comb 50	Huminsulin® Profil III	Mixtard® 30
Premixed insulin with insulin analogs (NPH-insulin plus 25-70% short-acting insulin analogs)	-	Humalog® Mix 25 Humalog® Mix 50	NovoMix® 30 NovoMix® 50
Long-acting and short acting insulinanalogue	-	-	70% Degludec plus 40% Aspart (Ryzodeg®)

Table 3 – Overview on the commonly used insulins in Austria and the European Union according to the OEDG (adjusted from 49)

1.2.3.2. Treatment of type 1 diabetes

T1D is characterized by loss of function of the beta cells of the pancreas, and thus, is characterized in a loss of insulin production. The essential therapy therefore is insulin substitution (55).

The comprehensive training of people with T1D which includes discussing the necessary measures and, subsequently, promoting self-competence is the basis for the successful implementation of the therapy. Specialized centers should provide trainings in diabetes management.

Standard insulin therapy today is functional insulin therapy (basal-bolus insulin therapy). For this therapy, basal insulin is used once or twice a day and bolus insulin is used with meals and, if necessary, to correct elevated glucose values (64).

Another variant of insulin therapy is insulin pump therapy in which short-acting insulins and short-acting insulin analogues are continuously administered subcutaneously via an externally attached insulin infusion pump, with what that the insulin requirement is covered. The pump's basal rate is programmed depending on individual basal insulin requirements and thus replaces the administration of long-acting and ultra long-acting basal insulins otherwise used in basal-bolus insulin therapy. If a bolus dose for normalization of glucose levels is needed, an individually calculated and situation-adapted bolus of short-acting insulin can be delivered at the push of a button (73,74).

Glucose levels should be measured regularly in order to be able to control the necessary insulin dose as precisely as possible. SMBG or CGM is used for that. By combining CGM with an insulin infusion pump in the sense of a hybrid closed-loop therapy (also called artificial pancreas or automated insulin delivery (AID) system)) can be used (73,75). This might be the most frequently used system in people living with T1D in the coming years (depending on financial resources of the respective healthcare systems and individuals living with diabetes). Glycemic derailments can also be reduced by diabetes-specific nutrition training by dietitians.

Also, the effects of alcohol consumption and smoking and the effect of sufficient physical activity and recommendations regarding the management of stress and illness are useful in a good therapy (75). Thus, food intake and exercise has a relevant effect on glycemic control not only in type 2 diabetes but also in type 1 diabetes.

2. Material and Methods

2.1. Study design

The current study is based on a retrospective data analysis. It is a registry study in people living with T1D using intermittently-scanned glucose monitoring (isCGM), also called Flash glucose monitoring in routine care for at least six months before the first studied time period started.

All participants were under routine care at the Department of Internal Medicine, Division of Endocrinology and Diabetology at the Medical University of Graz. Eligible people with type 1 diabetes were included in the registry following informed consent procedure. A register participant number was assigned to each participant in an ascending order. Three dates of time periods were selected as following:

- Pre-lockdown (same season): 16.03.2019 – 16.06.2019
- Pre-lockdown: 01.12.2019 – 29.02.2019
- Lockdown: 16.03.2020 – 16.06.2020

Data from those time periods were taken under closer investigation and compared to each other to arrive at a statement on glycemic control, and to compare clinical visits during those periods. The first period was set in a time referred to the first Austrian-wide lockdown in 2020. The second period was set to the time recently before lockdown started and the third period was set one year before first Austrian-wide lockdown started.

No status of whether being infected with COVID-19 or not was investigated. Since the vaccination was not released at the time, also the status of vaccination was of no interest and omitted for this study.

2.1.1. Selection of participants

As FreeStyle Libre 1 was widely used in the time when the study was performed, all participants of the current study were using Abbott's FreeStyle Libre 1 in combination with Abbot's FreeStyle LibreLink App[3] software (76). The study included both male and female participants that were at least 18 years old with an established diagnosis of type 1 diabetes. They were using either an insulin pump therapy or multiple daily injection regimens for at least six months prior to the first study period. Furthermore, they had consistent data available for

HbA1c and creatinine levels in the electronic medical records of the hospital (MEDOCS). People with cognitive dysfunction rendering the individual incapable of signing the informed consent were not included.

2.1.2. Informed consent

Informed consent, written in accordance with the origins of the Declaration of Helsinki and the applicable laws of Austria was obtained prior to inclusion into the registry. The responsible physician explained the nature, purpose, and risk of the registry study, provided the candidates with a copy of the subject information sheet, and asked for a written consent before she or he was included in the registry.

2.1.3. Ethical issues

The registry was submitted and approved by the Ethics Committee of the Medical University of Graz. (ethics number 29-522 ex 16/17).

2.1.4. Source documents

All individuals meeting the above mentioned criteria with availability of required data were included in the analysis. Data was obtained from the data base of the diabetes outpatient clinic at Medical University of Graz. Data on intermittently-scanned continuous glucose monitoring was downloaded from the database of Abbott's FreeStyle Libre (76). Search of electronic medical data base of the hospital (Medocs) with focus on outpatient clinic visits was performed. The number of outpatient clinic visits, phone contacts and emergency room admissions related to diabetes was documented. Diabetes-related data (HbA1c, type of therapy, diabetes duration) and biometric data (weight, height, BMI, age, gender) were collected. Data on glucose metrics from Abbott FreeStyle Libre were obtained as csv files from the FreeStyle LibreView system.

2.1.5. Study hypothesis

H0: The COVID-19 pandemic does not negatively affect glycemic control in people living with type 1 diabetes due to a reduction of outpatient clinic visits and elevated stress levels.

H1: The COVID-19 pandemic negatively affects glycemic control in people living with type 1 diabetes due to a reduction in outpatient clinic visits and elevated stress levels.

2.2. Study objectives

The aim of the present study is to assess the effect of the COVID-19 pandemic on glycemic control in people living with type 1 diabetes using intermittently scanned continuous glucose monitoring. We wanted to evaluate if glycemic goals such as sufficient time in range whilst also keeping time above and below range were achieved during the pandemic. By that, the impact of the lockdown period on glycemic control in people living with type 1 diabetes was evaluated. Further, we compared outpatient clinic visits during three periods.

For the study, the three time periods were determined and data of those were compared retrospectively.

A main and sensitivity analysis was performed. The main analysis includes only individuals for whom data for all 3 phases were available. Sensitivity analysis includes all individuals with isCGM data in at least 2 phases of which one had to be in lockdown and for whom baseline data is available.

2.2.1. Statistics

isCGM measurement data was downloaded from Abbott's FreeStyle Libre database as comma-separated values data (CSV). documents, anonymized by the ascending register number and further processed by Microsoft Excel version 16.78.3 (23102801). Statistical analysis was done with R version 4.3.1 (2023-06-16).

Main and sensitivity analysis was performed. The main analysis includes only individuals with all three phases for whom baseline data are available. The sensitivity analysis includes all individuals with isCGM data in at least two phases of which one had to be lockdown and for whom baseline data were available. All data that was calculated was drawn to the reference date 16.06.2020 – when period three finished. Because of the exploratory nature of this study, descriptive analyses were performed.

Baseline analysis includes numeric variables: age (years), diabetes duration (years), height (m), weight (kg), BMI (kg/m^2), HbA1c (mmol/mol), creatinine (mg/dL), FreeStyle Libre 1 use duration (months and years) and visits (number) during lockdown, pre-lockdown and pre-lockdown (same season).

Baseline analysis also includes following categorical variables: diabetes type, gender, and pen/pump use.

Glucose parameters were evaluated as followed: N study days, N isCGM values, mean glucose, coefficient of variation (CV – the percentage of the average of the standard deviation),

glucose management indicator (GMI – estimates what the approximate HbA1c level might be and is based on the average glucose level from your CGM data readings for more than 14 days), mean amplitude of glycemic excursions (MAGE – the arithmetic mean of the difference between consecutive glycemic minimal and maximal values) for each period (77). Times in different ranges were evaluates as followed: <54 mg/dL, 54 - <70 mg/dL, 70 - 180 mg/dL, >180 - 250 mg/dL and >250 mg/dL.

For the main analysis, differences between the two pre-lockdown periods to lockdown were calculated for each participant and then summarized (note that this is only feasible for the main analysis). This was done for glucose parameter and times in certain ranges.

Scan frequencies were evaluated in the total number of scans per person during each phase. Scan frequency per day is the mean daily scan frequency per person during each phase.

3. Results

Main and sensitivity analyses were performed. Because of the exploratory nature of this study, descriptive analyses were done. The main analysis includes individuals with all three phases for whom baseline data are available. The sensitivity analysis includes all individuals with isCGM data in at least two phases of which one had to be lockdown and for whom baseline data are available. Baseline characteristics are presented as median (Q1-Q3) for numeric variables and n (%) for categorical variables. For each period, the following glucose parameters were calculated: isCGM activity (n), mean glucose (mg/dL), CV, GMI, MAGE, time in different ranges (< 54 mg/dL, 54 - < 70 mg/dL, 70 - 180 mg/dL, > 180 - 250 mg/dL and > 250 mg/dL, respectively) as well as total and mean daily scan frequency. Summary statistics of parameters are presented for each period. CGM activity is calculated based on a nominal number of 96 CGM values per day (every 15 minutes). Note that activity can be higher than 100% because additional CGM values are saved for calibration or other reasons not documented by the CGM manufacturers.

3.1. N Phases

Table 16(1) can be found in the appendix and shows sample-IDs. Also, the number of phases and if baseline data is available and can be found in the same table.

3.1.1. Main analysis

The main analysis includes only subjects with all three phases for whom baseline data is available. Additionally, to the values analyzed in a comparable manner as in the sensitivity analysis, differences between the two pre-lockdown periods to lockdown were calculated for each participant and then summarized.

3.1.1.1. Baselines numeric (main analysis)

Table 4 the baselines of the numeric variables of the main analysis. All median values with interquartile ranges (IQR, Q1-Q3), mean values with standard deviation (SD) and minimum and maximum values of the numeric variables, age [years], diabetes duration [years], height [m], weight [kg], BMI [kg/m^2], HbA1c [mmol/mol], creatinine [mg/dL], isCGM use duration [months] [years] and visits [n] during each phase can be found.

Parameter	Median (Q1-Q3)	Mean ± SD	Min - Max
Age [years]	33.5 (26.3; 49.5)	37.8 ± 13.9	19.7 - 73.3
Diabetes duration [years]	13.5 (5.5; 22.0)	16.9 ± 14.0	1.45 - 64.5
Height [m]	1.8 (1.7; 1.8)	1.8 ± 0.1	1.6 - 1.9
Weight [kg]	76.0 (68.0; 88.3)	77.6 ± 14.3	49.0 - 134.0
BMI [kg/m^2]	24.6 (22.3; 27.0)	24.7 ± 3.7	18.4 - 37.9
HbA1c [mmol/mol]	58.5 (51.0; 69.3)	60.9 ± 13.2	37.0 - 100.0
Creatinine [mg/dL]	0.9 (0.8; 1.0)	1.0 ± 0.5	0.6 - 4.4
isCGM use duration [months]	68.5 (58.0; 79.3)	68.8 ± 12.0	51.0 - 92.0
isCGM use duration [years]	5.7 (4.8; 6.6)	5.7 ± 1.0	4.3 - 7.7
Visits during lockdown [n]	0.0 (0.0; 1.0)	0.5 ± 1.1	0.0 - 6.0
Visits during pre-lockdown [n]	1.0 (0.0; 1.0)	1.0 ± 1.5	0.0 - 6.0
Visits during pre-lockdown (same season) [n]	1.0 (0.0; 2.3)	1.6 ± 2.1	0.0 - 11.0

Table 4 – Main analysis: baselines (numeric variables)(1)

3.1.1.2. Baselines categorical (main analysis)

Categoric variables of the main analysis are shown in Table 5. The categorical variables diabetes type, gender type and if pen or pump system is in use can be found in form of number (n) and percent (%).

Parameter	Level	Number (n)	Percent %
Diabetes type	T1D	64	100
	missing	0	0
Gender	female	22	34,4
	male	42	65,6
	missing	0	0
Pen/pump	pen	48	75
	pump	16	25
	missing	0	0

Table 5 –Main analysis: baselines (categorical variables)(1)

3.1.1.3. isCGM parameters (main analysis)

Table 6 shows the differences in the certain phases and number of individuals (n). The parameters days (n), isCGM values (n), mean glucose (mg/dL), CV, GMI and MAGE are shown on base of median values with IQR and mean values with SD as well as minimum and maximum values for each phase separately. 93 days were included within lockdown period and pre-lockdown period (same season). Pre lockdown period had 91 days. isCGM value was highest in pre-lockdown (same season) but nearly same than lockdown period. Pre-lockdown period had less isCGM values, but it also had two days less that were investigated. Mean glucose was 176.5mg/dL and thus highest in pre-lockdown (same season) CV was same for all periods, GMI and MAGE were highest in pre-lockdown (same season).

Phase	Individuals (n)	Parameter	Median (Q1-Q3)	Mean ± SD	Min – Max
Lockdown	63	Days (n)	93.00 (90.00; 93.00)	87.32 ± 15.70	6.00 - 93.00
		isCGM values (n)	8308.00 (7245.50; 8480.00)	7570.1 ± 2000.4	155.00 - 12934.00
		Mean glucose (mg/dL)	163.6 (154.1; 193.1)	176.5 ± 42.6	112.4 - 352.0
		CV	0.4 (0.3; 0.4)	0.4 ± 0.1	0.2 - 0.6
		GMI	7.2 (7.0; 7.9)	7.5 ± 1.0	6.0 - 11.7
		MAGE	177.51 (163.5; 202.4)	187.2 ± 41.9	119.0 - 357.8
Pre-lockdown	63	Days (n)	91.0 (85.5; 91.0)	83.1 ± 18.0	4.0 - 91.0
		isGCM values (n)	8009.0 (6875.0; 8357.0)	7205.3 ± 2021.7	143.0 - 10312.0
		Mean glucose (mg/dL)	168.4 (154.9; 197.0)	180.1 ± 37.6	113.9 - 299.4
		CV	0.4 (0.3; 0.4)	0.4 ± 0.1	0.2 - 0.5
		GMI	7.3 (7.0; 8.0)	7.6 ± 0.9	6.0 - 10.5

		MAGE	177.0 (165.4; 205.7)	189.4 ± 38.8	121.3 - 358.0
Pre-lockdown (same season)	63	Days (n)	93.00 (85.00; 93.00)	80.03 ± 24.21	5.00 - 93.00
		isCGM values (n)	8311.0 (5804.5; 8677.5)	7027.4 ± 2361.2	399.0 - 9177.0
		Mean glucose (mg/dL)	176.5 (155.9; 196.1)	180.1 ± 34.3	117.6 - 275.8
		CV	0.4 (0.4; 0.4)	0.4 ± 0.1	0.2 - 0.5
		GMI	7.5 (7.0; 8.0)	7.6 ± 0.8	6.1 - 9.9
		MAGE	187.3 (170.5; 207.9)	190.3 ± 32.7	123.9 - 286.1

Table 6 – Main analysis: isCGM parameters(1)

The differences between the periods (lockdown vs. pre-lockdown and lockdown vs. pre-lockdown (same season) are shown based on the same values and can be found in Table 7. Lockdown vs. pre-lockdown comparison showed more differences than lockdown vs. pre-lockdown (same season) comparison.

Difference	**Parameter**	**Median (Q1-Q3)**	**Mean ± SD**	**Min - Max**
Lockdown vs. pre-lockdown	Days (n)	0.00 (0.00; 1.50)	7.29 ± 27.54	-87.00 - 88.00
	isCGM values (n)	-42.00 (-471.00; 1247.00)	542.70 ± 2655.96	-8701.00 - 7699.00
	isCGM activity	-1.02 (-5.93; 1.19)	-3.18 ± 14.39	-72.28 - 42.17
	Mean glucose (mg/dL)	-3.60 (-17.19; 6.29)	-3.68 ± 22.38	-42.86 - 83.03
	CV	-0.02 (-0.05; 0.00)	-0.02 ± 0.04	-0.16 - 0.13
	GMI	-0.09 (-0.41; 0.15)	-0.09 ± 0.54	-1.03 - 1.99
	MAGE	-6.47 (-17.06;	-3.10 ± 23.50	-43.34 - 94.87

		8.66)		
Lockdown vs. pre-lockdown (same season)	Days (n)	2.00 (2.00; 2.00)	4.19 ± 14.04	-56.00 - 66.00
	isCGM values (n)	185.00 (-2.00; 577.50)	364.76 ± 1301.34	-5645.00 - 4181.00
	isCGM activity	0.00 (-1.71; 1.63)	0.12 ± 11.74	-70.54 - 27.11
	Mean glucose (mg/dL)	-3.78 (-13.48; 2.56)	-3.59 ± 18.31	-61.59 - 66.91
	CV	-0.01 (-0.03; 0.00)	-0.01 ± 0.03	-0.12 - 0.11
	GMI	-0.09 (-0.32; 0.06)	-0.09 ± 0.44	-1.47 - 1.60
	MAGE	-2.26 (-11.77; 3.67)	-2.16 ± 20.42	-74.97 - 80.82

Table 7 – Main analysis: differences of isCGM data in phases(1)

3.1.1.4. Time in different ranges (main analysis)

Table 8 show the time in certain glucose ranges of all three phases. Times in glucose ranges of < 54 mg/dL, 54 - < 70 mg/dL, 70 - 180 mg/dL, > 180 - 250 mg/dL and > 250 mg/dL are shown on base of median with IQR, mean with SD and minimum and maximum values. In all three phases, TIR (70-180 mg/dL) was highest whereby lockdown delivered best data. Also concerning TBR and TAR lockdown phase had best values.

Phase	Glucose ranges	Median (Q1-Q3)	Mean ± SD	Min - Max
Lockdown	< 54 mg/dL	0.2 (0.1; 0.8)	0.6 ± 0.9	0.0 - 5.0
	54 - < 70 mg/dL	2.0 (0.7; 4.7)	3.1 ± 2.9	0.0 - 13.4
	< 70 mg/dL	2.3 (0.8; 6.1)	3.6 ± 3.5	0.0 - 14.9
	70 - 180 mg/dL	57.4 (45.6; 66.8)	55.6 ± 17.8	3.7 - 92.2
	> 180 - 250 mg/dL	24.3 (21.2; 30.3)	24.9 ± 8.1	3.4 - 43.1
	> 180 mg/dL	35.4 (28.9; 53.3)	40.7 ± 19.2	3.4 - 96.3
	> 250 mg/dL	11.2 (5.5; 20.2)	15.9 ± 16.3	0.1 - 85.3
Pre-lockdown	< 54 mg/dL	0.7 (0.2; 1.7)	1.2 ± 1.4	0.0 - 6.5
	54 - < 70 mg/dL	2.6 (1.3; 4.0)	2.9 ± 2.2	0.0 - 10.5
	< 70 mg/dL	3.6 (1.6; 5.9)	4.1 ± 3.4	0.0 - 15.2

	70 - 180 mg/dL	54.7 (41.2; 66.1)	52.6 ± 17.4	12.6 - 87.4
	> 180 - 250 mg/dL	26.4 (21.9; 30.9)	26.1 ± 7.6	4.0 - 43.4
	> 180 mg/dL	40.6 (30.0; 56.1)	43.3 ± 18.5	4.5 - 87.4
	> 250 mg/dL	12.3 (6.3; 24.0)	17.1 ± 14.7	0.1 - 62.0
Pre-lockdown (same season)	< 54 mg/dL	1.0 (0.4; 2.3)	1.6 ± 1.8	0.0 - 8.3
	54 - < 70 mg/dL	2.8 (1.4; 4.3)	3.1 ± 2.3	0.0 - 11.2
	< 70 mg/dL	3.6 (1.8; 6.5)	4.7 ± 3.8	0.0 - 14.9
	70 - 180 mg/dL	51.5 (41.5; 60.9)	51.9 ± 16.0	19.8 - 85.5
	> 180 - 250 mg/dL	24.9 (21.7; 30.3)	25.6 ± 7.9	6.7 - 47.0
	> 180 mg/dL	44.6 (31.5; 55.2)	43.5 ± 17.3	7.2 - 80.0
	> 250 mg/dL	15.0 (8.6; 23.3)	17.9 ± 13.5	0.3 - 55.9

Table 8 – Main analysis: time in different ranges(1)

Figure 5 underlines the findings of Table 8. Time in ranges in presented on the y-axis and the certain periods can be found on the x-axis. Lockdown period had the best glycemic control indicated by lowest percentage in TBR and TAR and highest percentage in TIR.

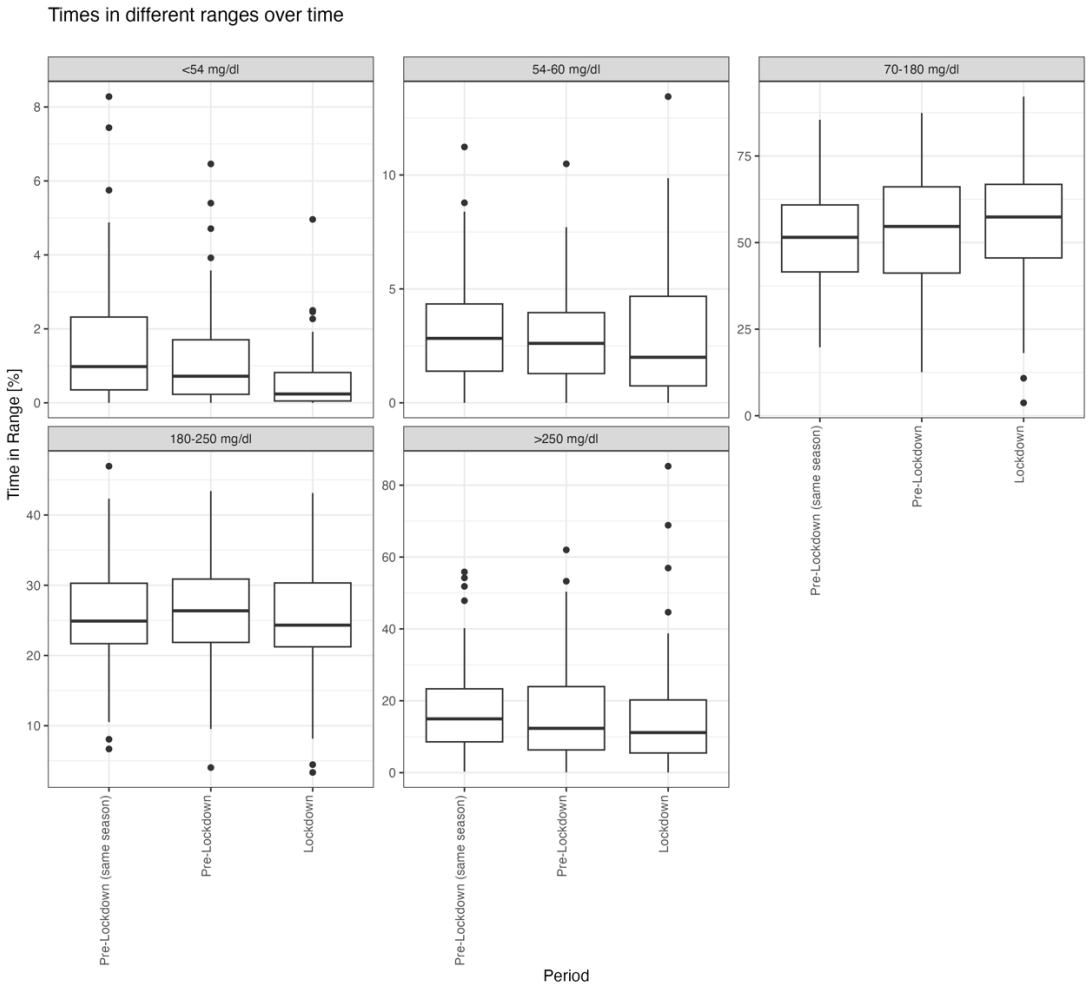

Figure 5 – Main analysis: boxplot of time in different ranges over time(1)

Table 9 gives an overview of the differences between the phases (lockdown vs. pre-lockdown and lockdown vs. pre-lockdown (same season) based on the same parameters. Concerning TIR, pre-lockdown data is closer to lockdown data. Same counts for TBR and TAR.

Difference	Parameter	Median (Q1-Q3)	Mean ± SD	Min - Max
Lockdown vs. pre-lockdown	< 54 mg/dL	-0.6 (-1.5; -0.1)	-1.0 ± 1.3	-5.0 - 1.9
	54 - < 70 mg/dL	-0.2 (-1.1; 0.6)	-0.1 ± 2.0	-6.4 - 6.4
	< 70 mg/dL	-1.2 (-2.4; 0.1)	-1.1 ± 2.3	-7.4 - 5.9
	70 - 180 mg/dL	3.2 (-1.7; 9.7)	3.8 ± 10.3	-20.0 - 27.7
	> 180 - 250 mg/dL	-0.5 (-3.2; 1.9)	-0.7 ± 6.3	-16.7 - 19.3
	> 180 mg/dL	-2.0 (-9.6; 2.1)	-2.7 ± 11.2	-27.7 - 21.0
	> 250 mg/dL	-1.8 (-5.2; 0.9)	-2.0 ± 7.9	-17.0 - 29.4

Lockdown vs. pre-lockdown (same season)	< 54 mg/dL	-0.4 (-1.0; -0.1)	-0.6 ± 0.9	-3.7 - 1.4
	54 - < 70 mg/dL	-0.1 (-0.6; 1.1)	0.2 ± 1.7	-4.9 - 4.9
	< 70 mg/dL	-0.3 (-1.4; 0.7)	-0.5 ± 1.9	-6.3 - 6.3
	70 - 180 mg/dL	3.9 (-1.6; 7.1)	3.0 ± 8.4	-19.0 - 23.7
	> 180 - 250 mg/dL	-1.2 (-3.76; 1.02)	-1.3 ± 5.2	-16.8 - 18.1
	> 180 mg/dL	-3.0 (-7.25; 0.96)	-2.6 ± 8.9	-30.0 - 20.0
	> 250 mg/dL	-0.9 (-4.14; 0.68)	-1.3 ± 6.6	-26.4 - 23.3

Table 9 – Main analysis: differences of time in different ranges(1)

Figure 6 presents the glucose ranges on the y-axis and the difference of time in range during lockdown on the x-axis. Differences in pre-lockdown and pre-lockdown (same season) to the lockdown period can be found.

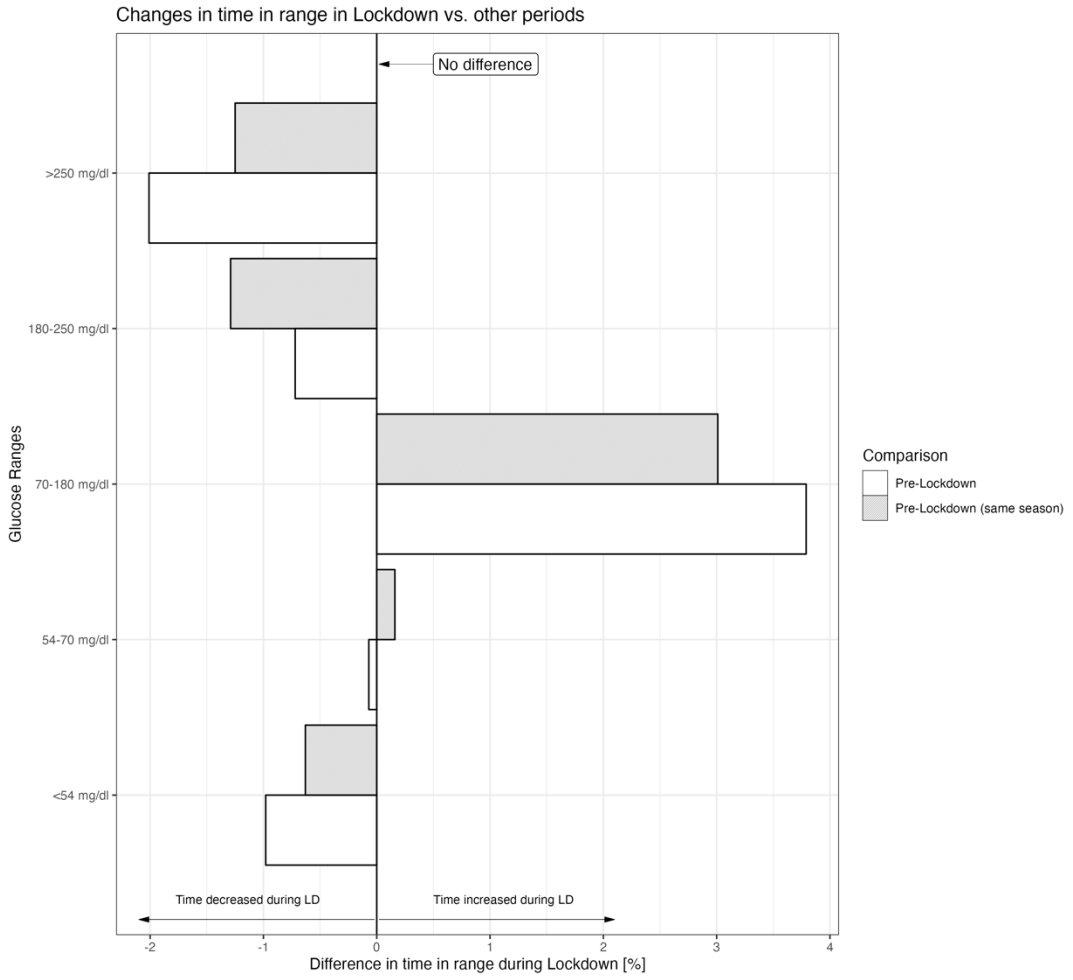

Figure 6 – Main analysis: changes in time in certain ranges (lockdown vs. other periods)(1)

3.1.1.5. Scan frequency (main analysis)

Table 10 shows the total number of daily scans during each phase and mean number of scans during each study phase. Median with IQR and mean values with SD as well as minimal and maximal values are shown for each phase analyzed. The number of daily scans was higher in the pre-lockdown period (same season) compared to the other two periods. Within the pre-lockdown period and the lockdown period there was nearly no difference.

Parameter	Phase	Median (Q1-Q3)	Mean ± SD	Min - Max
Total isCGM scan frequency	Lockdown	814.0 (551.0; 1204.5)	979.9 ± 706.9	7.0 - 3805.0
	Pre-lockdown	817.0 (610.0; 1163.0),	964.0 ± 684.1	9.0 - 4193.0
	Pre-lockdown-(same season)	899.0 (481.0 1430.5)	1082.3 ± 760.8	97.0 - 3961.0
Mean daily isCGM scan frequency	Lockdown	8.8 (6.3; 13.0)	10.8 ± 7.5	1.2 - 40.9
	Pre-lockdown	9.1 (6.8; 13.8)	11.3 ± 7.6	1.9 - 46.1
	Pre-lockdown-(same season)	11.5 (7.8; 19.4)	14.1 ± 9.0	1.8 - 42.6

Table 10 – Main analysis: scan frequencies(1)

Figure 7 and Figure 8 shows a boxplot model of the scan frequencies. With that, again, it can be stated that scan frequencies were highest during pre-lockdown (same season).

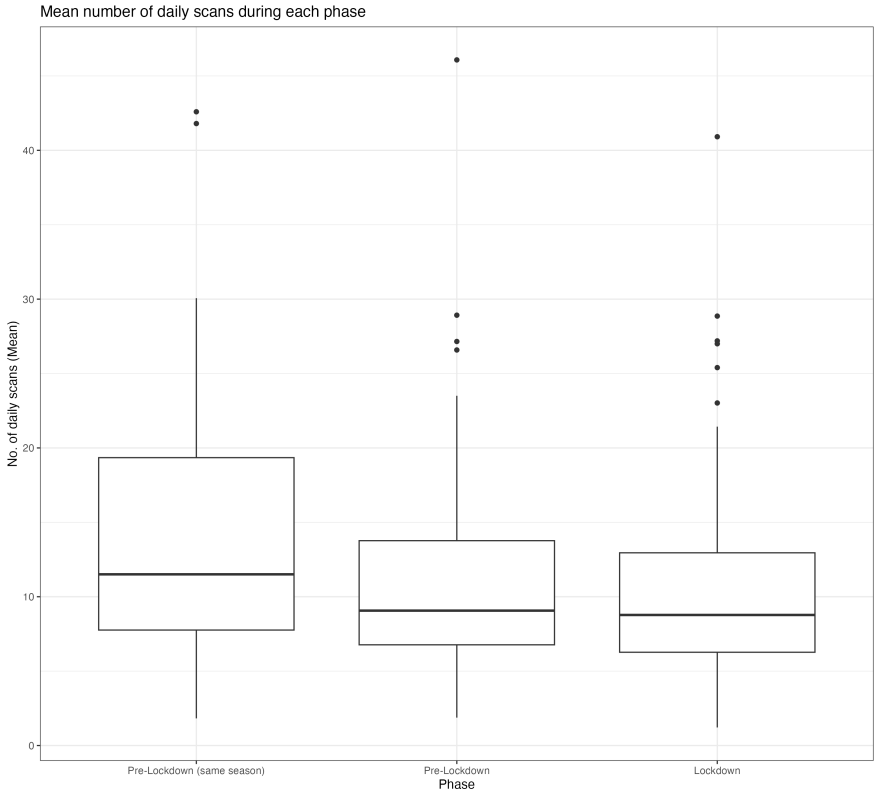

Figure 7 – Main analysis: mean number of daily scans during each phase(1)

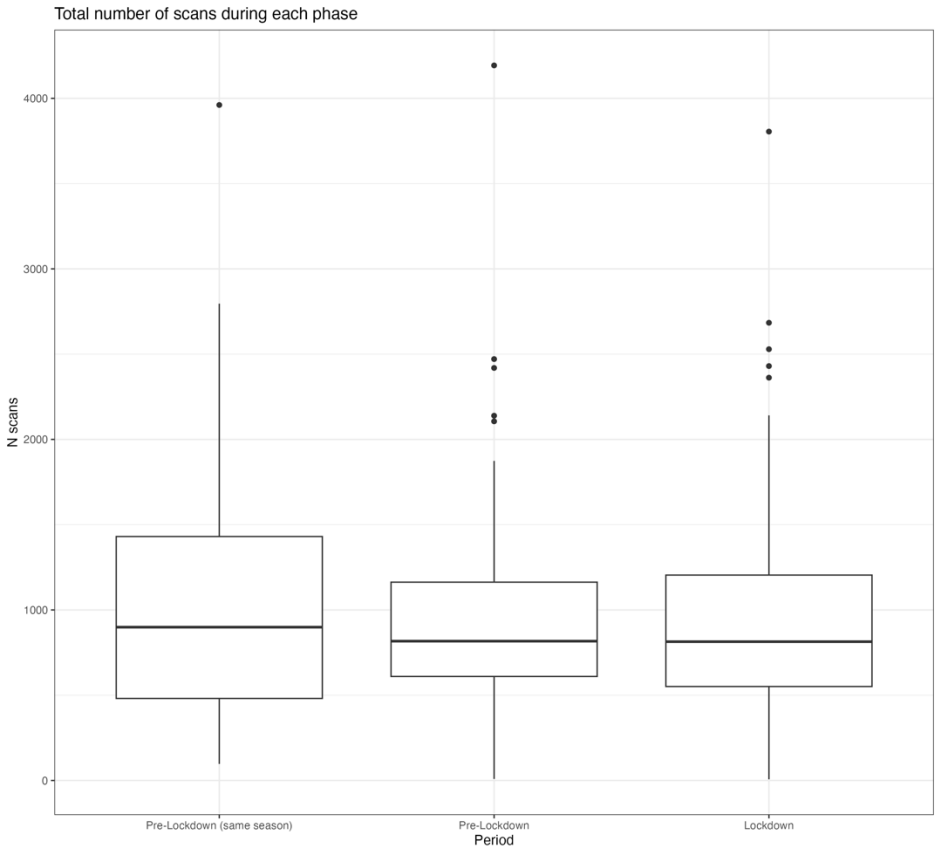

Figure 8 – Main analysis: total number of scan frequencies during each phasese(1)

3.1.2. Sensitivity Analysis

Beside the main analysis also a sensitivity analysis was performed. The sensitivity analysis includes all subjects with CGM data in at least two phases of which one had to be lockdown and for whom baseline data are available.

3.1.2.1. Baselines numeric (sensitivity analysis)

Table 11 shows the baselines of the numeric variables of the sensitivity analysis. All median values with interquartile ranges (IQR, Q1-Q3), mean values with standard deviation (SD) and minimum and maximum values of the numeric variables, age [years], diabetes duration [years], height [m], weight [kg], BMI [kg/m^2], HbA1c [mmol/mol], creatinine [mg/dL], isCGM use duration [months] [years] and visits [n] during each phase can be found.

Parameter	Median (Q1-Q3)	Mean ± SD	Min - Max
Age [years]	33.2 (25.5; 49.1)	36.9 ± 13.6	19.2 - 73.3
Diabetes duration [years]	12.5 (5.5; 20.7)	15.7 ± 13.7	1.5 - 64.5
Height [m]	1.8 (1.7; 1.8)	1.8 ± 0.1	1.5 - 1.9
Weight [kg]	76.0 (68.0; 88.3)	76.9 ± 14.9	43.0 - 134.0
BMI [kg/m^2]	24.0 (22.0; 26.9)	24.4 ± 3.8	17.4 - 37.9
HbA1c [mmol/mol]	57.5 (51.0; 69.3)	61.3 ± 16.1	37.0 - 143.0
Creatinine [mg/dL]	0.9 (0.8; 1.0)	0.9 ± 0.4	0.6 - 4.4
isCGM use duration [months]	67.0 (55.0; 79.0)	67.1 ± 12.9	47.0 - 92.0
isCGM use duration [years]	5.6 (4.6; 6.6)	5.6 ± 1.1	3.9 - 7.7
Visits during lockdown [n]	0.0 (0.0; 1.0)	0.5 ± 1.2	0.0 - 6.0
Visits during pre-lockdown [n]	1.0 (0.0; 1.0)	1.2 ± 1.7	0.0 - 7.0
Visits during pre-lockdown (same season) [n]	1.0 (0.0; 2.0)	1.5 ± 2.3	0.0 - 11.0

Table 11 – Sensitivity analysis: baselines (numeric variables)(1)

3.1.2.2. Baselines categorical (sensitivity analysis)

Categoric variables of the Sensitivity analysis are shown in Table 12. The categorical variables diabetes type, gender type and if pen or pump system is in use can be found in form of number (n) and percent (%).

Parameter	Level	Number (n)	Percent (%)
Diabetes type	T1D	80	100
	missing	0	0
Gender	female	26	32,5
	male	54	67,5
	missing	0	0
Pen/pump	pen	60	75
	pump	20	25
	missing	0	0

Table 12 – Sensitivity analysis: baselines (categorical variables)(1)

3.1.2.3. isCGM parameters (sensitivity analysis)

Table 13 shows the differences in the certain phases and number of individuals (n). The parameters days (n), isCGM values (n), mean glucose (mg/dL), CV, GMI and MAGE are shown on base of median values with IQR and mean values with SD as well as minimum and maximum values for each phase separately. 79 individuals and 93 days were in included in lockdown phase, 78 individuals and 91 days in pre-lockdown phase and 64 individuals and 93 days in pre-lockdown (same season) phase. Pre-lockdown period had – same than in main analysis – less isCGM values, but also two days less that were investigated. Mean glucose was highest (177.7 mg/dL) in pre-lockdown (same season). CV was same for all periods, GMI and MAGE were highest in pre-lockdown (same season).

Phase	Individuals (n)	Parameter	Median (Q1-Q3)	Mean ± SD	Min – Max
Lockdown	79	Days (n)	93.0 (90.0; 93.0)	86.9 ± 17.2	1.0 - 93.0
		isCGM values (n)	8283.0 (7349.5; 8478.0)	7521.1 ± 2027.0	32.0 - 12934.0
		Mean glucose (mg/dL)	163.2 (150.6; 193.0)	174.4 ± 42.4	110.4 - 352.0
		CV	0.4 (0.3; 0.4)	0.37±0.07	0.2 - 0.6
		GMI	7.2 (6.9; 7.9)	7.4 ± 1.0	6.0 - 11.7
		MAGE	175.7 (162.4;	184.9 ± 40.9	119.0 -

			197.6)		357.8
Pre-lockdown	78	Days (n)	91.0 (82.5; 91.0)	82.6 ± 18.2	4.0 - 91.0
		isCGM values (n)	7930.0 (6646.3; 8344.5)	7104.0 ± 2015.0	143.0 - 10312.0
		Mean glucose (mg/dL)	166.7 (154.0; 195.3)	177.0 ± 38.8	107.8 - 299.4
		CV	0.4 (0.3; 0.4)	0.4 ± 0.1	0.2 - 0.5
		GMI	7.3 (7.0; 8.0)	7.5 ± 0.9	5.9 - 10.5
		MAGE	175.4 (164.3; 203.9)	186.8 ± 39.3	121.3 - 358.0
Pre-lockdown (same season)	64	Days (n)	93.0 (85.5; 93.0)	80.2 ± 24.1	5.0 - 93.0
		isCGM values (n)	8309.0 (5829.8; 8675.3)	7039.9 ± 2344.5	399.0 - 9177.0
		Mean glucose (mg/dL)	177.7 (156.2; 195.7)	180.1 ± 34.1	117.6 - 275.8
		CV	0.4 (0.4; 0.4)	0.4 ± 0.1	0.2 - 0.5
		GMI	7.6 (7.1; 8.0)	7.6 ± 0.8	6.1 - 9.9
		MAGE	187.5 (170.8; 207.8)	190.3 ± 32.5	123.9 - 286.1

Table 13 – Sensitivity analysis: isCGM parameters(1)

3.1.2.4. Time in different ranges (sensitivity analysis)

Table 14 show the time in certain glucose ranges of all three phases. Times in glucose ranges of < 54 mg/dL, 54 - < 70 mg/dL, 70 - 180 mg/dL, > 180 - 250 mg/dL and > 250 mg/dL are shown on base of median with IQR, mean with SD and minimum and maximum values. In all three phases, TIR (70-180 mg/dL) was highest whereby lockdown delivered best data. Also concerning TBR and TAR lockdown phase had best values.

Phase	Glucose range	Median (Q1-Q3)	Mean ± SD	Min - Max
Lockdown	< 54 mg/dL	0.2 (0.1; 0.8)	0.6 ± 1.0	0.0 - 5.0
	54 - < 70 mg/dL	2.0 (0.8; 5.4)	3.2 ± 2.9	0.0 - 13.4
	< 70 mg/dL	2.3 (0.8; 6.4)	3.8 ± 3.6	0.0 - 14.9
	70 - 180 mg/dL	58.4 (45.4; 68.4)	56.8 ± 18.5	3.7 - 92.2
	> 180 - 250 mg/dL	24.3 (20.7; 28.5)	23.9 ± 8.6	3.4 - 43.1
	> 180 mg/dL	35.3 (27.9; 52.9)	39.4 ± 19.6	3.4 - 96.3
	> 250 mg/dL	10.0 (4.9; 20.7)	15.6 ± 16.5	0.1 - 85.3
Pre-lockdown	< 54 mg/dL	0.7 (0.3; 1.8)	1.3 ± 1.5	0.0 - 7.7
	54 - < 70 mg/dL	2.8 (1.4; 4.3)	3.1 ± 2.6	0.0 - 13.9
	< 70 mg/dL	3.7 (1.7; 6.1)	4.4 ± 3.9	0.0 - 18.7
	70 - 180 mg/dL	55.7 (41.9; 67.5)	54.3 ± 18.0	12.6 - 90.6
	> 180 - 250 mg/dL	24.7 (21.0; 29.7)	24.9 ± 8.1	4.0 - 43.4
	> 180 mg/dL	38.7 (29.3; 55.8)	41.2 ± 19.1	4.5 - 87.4
	> 250 mg/dL	11.6 (4.6; 24.1)	16.4 ± 14.9	0.0 - 62.0
Pre-lockdown (same season)	< 54 mg/dL	0.9 (0.4; 2.3)	1.5 ± 1.8	0.0 - 8.3
	54 - < 70 mg/dL	2.8 (1.5; 4.3)	3.1 ± 2.3	0.0 - 11.2
	< 70 mg/dL	3.6 (1.9; 6.5)	4.7 ± 3.8	0.0 - 14.9
	70 - 180 mg/dL	51.6 (41.7; 60.8)	51.9 ± 15.8	19.8 - 85.5
	> 180 - 250 mg/dL	25.2 (21.7; 30.2)	25.6 ± 7.9	6.7 - 47.0
	> 180 mg/dL	44.7 (31.8; 55.1)	43.5 ± 17.1	7.2 - 80.0
	> 250 mg/dL	15.3 (8.7; 23.2)	17.8 ± 13.4	0.3 - 55.9

Table 14 – Sensitivity analysis: time in different ranges(1)

Figure 9 confirms the statement that Table 14 delivers. Time in ranges is presented on the y-axis and the certain periods can be found on the x-axis. Lockdown period has lowest results in TBR and TAR and highest in TIR which is the goal of isCGM.

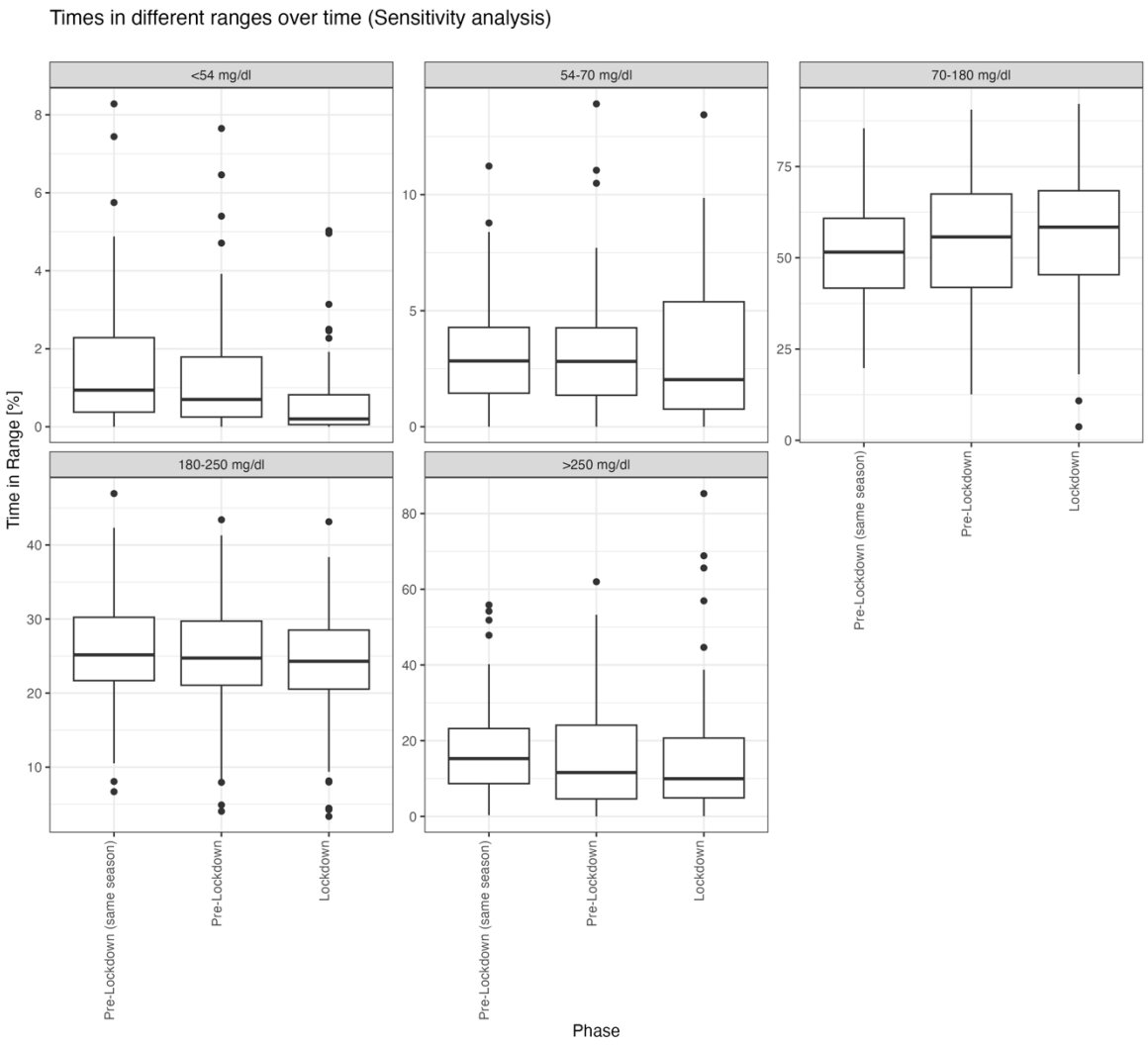

Figure 9 – Sensitivity analysis: boxplot of times in different ranges over time(1)

3.1.2.5. Scan frequency (sensitivity analysis)

Table 15 shows the total number of daily scans during each phase and mean number of scans during each study phase. Median with IQR and mean values with SD as well as minimal and maximal values are shown for each phase analyzed. The number of daily scans was higher in the pre-lockdown period (same season) compared to the other two periods. Within the pre-lockdown period and the lockdown period there was nearly no difference.

Parameter	Phase	Median (Q1-Q3)	Mean ± SD	Min - Max
Total isCGM scan	Lockdown	816.0 (567.0; 1261.0)	1002.9 ± 724.6	2.0 - 3805.0

frequency				
	Pre-lockdown	810.5 (553.8; 1172.0)	991.3 ± 761.5	9.0 - 4193.0
	Pre-lockdown-(same season)	900.0 (483.5; 1426.8)	1082.3 ± 754.7	97.0 - 3961.0
Mean daily isCGM scan frequency	Lockdown	8.9 (6.4; 13.6)	11.0 ± 7.7	1.2 - 40.9
	Pre-lockdown	9.2 (6.7; 14.7)	11.8 ± 8.4	1.9 - 46.1
	Pre-lockdown (same season)	11.6 (7.8; 19.3)	14.0 ± 8.9	1.8 - 42.6

Table 15 – Sensitivity analysis: scan frequency(1)

Figure 10 and Figure 11 show that also scan frequencies of sensitivity analysis were highest during pre-lockdown (same season).

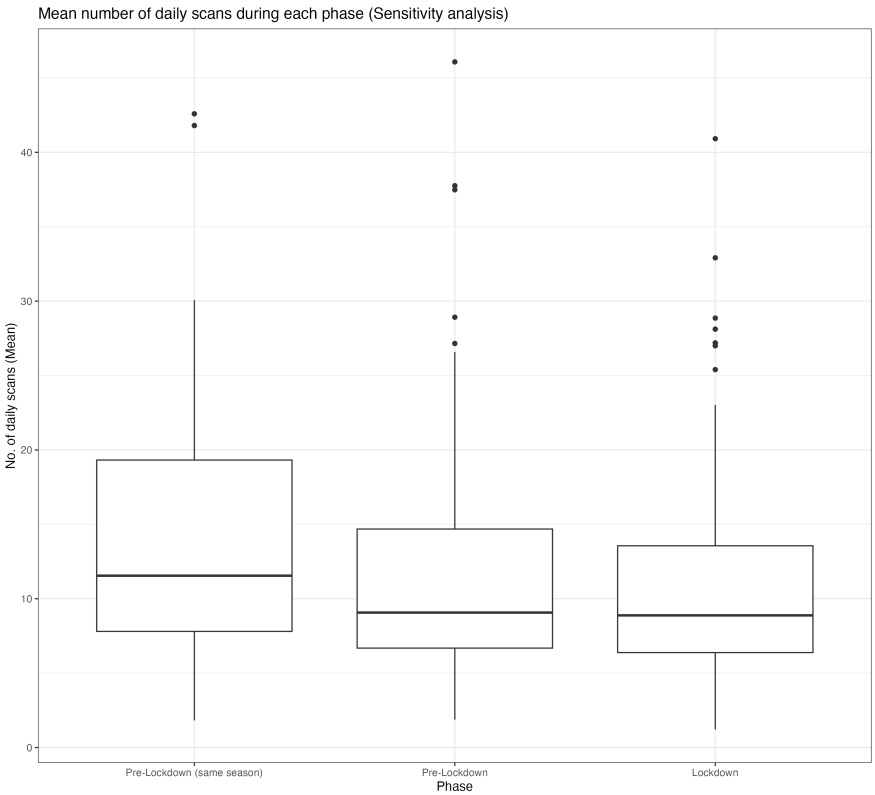

Figure 10 – Sensitivity analysis: mean number of daily scans during each phase(1)

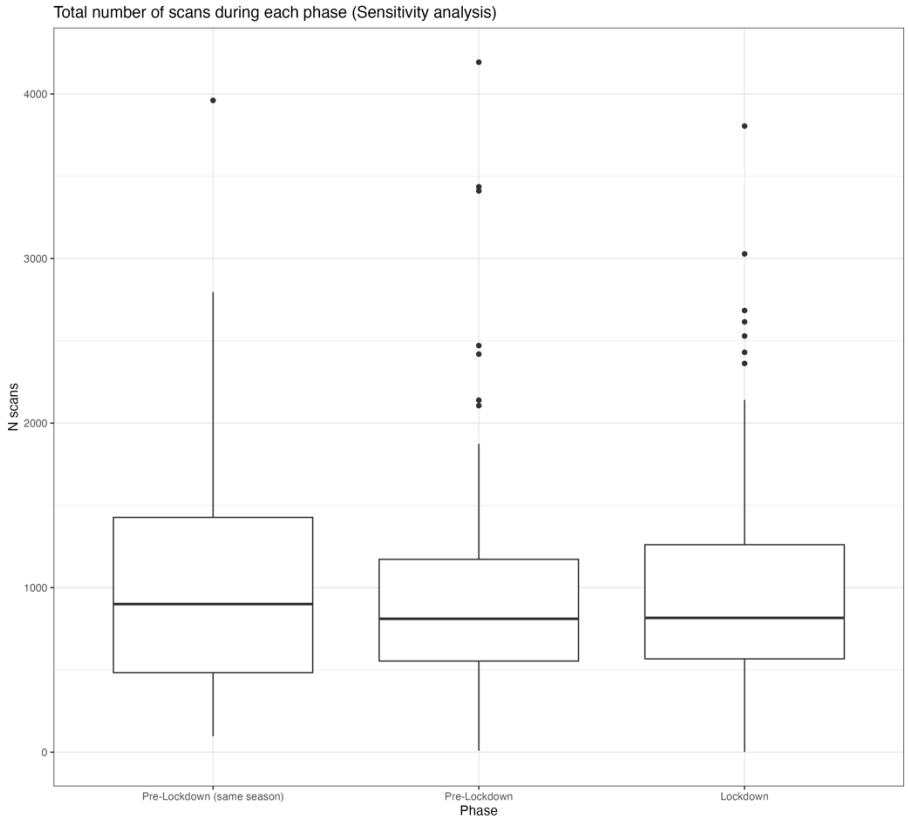

Figure 11 – Sensitivity analysis: total number of scan frequencies during each phase(1)

4. Discussion

The aim of the current analysis was do assess glycemic control before and during the COVID-19 pandemic. Therefore, a register study with retrospective data analysis was performed. Descriptive analyses were done. Data of people with T1D using isCGM of Abbott FreeStyle Libre 1 system were investigated retrospectively. We took closer under investigation whether the COVID-19 pandemic negatively affects glycemic control in people with T1D due to reduction in outpatient clinic service and elevated stress levels. Data was examined for three periods of three months each.

- Pre-lockdown (same season): 16.03.2019 – 16.06.2019
- Pre-lockdown: 01.12.2019 – 29.02.2019
- Lockdown: 16.03.2020 – 16.06.2020

The studies goal was to compare those time periods, to make a statement on glycemic control, to compare the time in certain ranges and frequency of clinical visits during those periods. No status of whether being infected with COVID-10 was investigated. Since the vaccination was not released in that time, also no status on vaccination was investigated.

A main analysis and a sensitivity analysis was performed. The main analysis included only subjects with all three phases for whom baseline data are available. The sensitivity analysis included all participants with isCGM data in at least two phases of which one must be lockdown and for whom baseline data are available. Focus of this work is set on the main analysis since it only includes subjects with data in all three phases. As data was not normally distributed, data is discussed on base of median with IQR. Mean and SD, minimum and maximum values were also calculated, but not investigated closer.

4.1. Baselines

Table 4 and Table 11 do not show strong deviations in the numeric variable diabetes duration. With that information it can be stated that they were used to the CGM system before pandemic started. Thus, they might have had a strong benefit compared to those who are lately diagnosed and felt left alone with their treatment within COVID-19 pandemic, as those individuals were less experienced than those with more experience in that field.

Concerning the clinical visits, it can be stated, that the number of visits was lower within lockdown. This – of course – is explained in the nature of the lockdown. Routine appointments were widely skipped. In the current study, there is no closer explanation weather the hospital visit was routinely or in emergency setting. This, of course, presents a strong limitation in the current analysis.

Table 5 and Table 12 confirm, that 100% of the participants of each study were people with T1D. No data from people with T2D were included in the current study. However, that might be interesting in following studies.

The division of males and females in this study does not have any background and was pure coincidence. However, as males have a minimal higher prevalence to develop diabetes it was likely, that there are more males than females in studies like that (16). In the current study, the number of males and females came by those which patients had consistent data for investigation.

Pump systems are more commonly used within individuals with diabetes and today are most commonly used therapy systems in patients with T1D (73,75). However, most patients that delivered data for the current study used pen diabetes systems. Firstly, this is reasoned in being already held in 2019, secondly, patients were not open for introducing new systems back then, as COVID-19 pandemic hit the whole world, and nobody knew a lot about it. However, for the current study, there might not be a difference in gained data if patients are using pen or pump system as all the participants were trained and used to the system in use.

4.2. isCGM parameters

The best glycemic control was observed during lockdown period – in both analyses. Table 6 and Table 13 show isCGM data in all three phases. Regarding the main analysis, the mean glucose was highest (176.5 mg/dL) within pre-lockdown (same season), decreased in pre-lockdown period (168.4 mg/dL) and finally was lowest in lockdown period (163.6 mg/dL). The difference of mean glucose was 3.6 mg/dL between lockdown and pre-lockdown period and 3.8 mg/dL between lockdown and pre-lockdown (same season) period. This difference is very small and simply underlines the findings explained above.

Sensitivity analysis delivered similar results. The mean glucose was highest during pre-lockdown period (same season) (177.7 mg/dL), decreased in pre lockdown period (166.7 mg/dL) and was lowest (163.20 mg/dL) within lockdown period.

That might be explained in a result of stress reduction, more time for diabetes management, cooking healthy food, more time for doing sports and walks in nature. In general, stress reduction within COVID-19 pandemic should not be underestimated and might be the main reason for the current results. In that field, further study is necessary.

4.3. Time in different ranges

Time in different glucose ranges were set at the following ranges, which is in line with the consensus statement: < 54 mg/dL, 54 - < 70 mg/dL, 70 - 180 mg/dL, > 180 - 250 mg/dL and > 250 mg/dL (49). This system was applied to main analysis in the same manner as it was to sensitivity analysis – and to all three phases each as Figure 9 and Table 14 show.

The most interesting fact is that the main analysis shows ascending TIR connected with descending TAR and TBR phases with time. TIR (70-180mg/dL) is ascending from pre-lockdown (same season) to pre-lockdown and to lockdown as well. TAR (>180mg/dL) decreased and TBR (<54mg/dL) decreased as well. This underlines the findings from the isCGM values those patients had a healthier and less stressful lifestyle within the pandemic, as the TIR raised in that phase.

Sensitivity analysis shows similar results. Pre-lockdown (same season) shows lower TIR than pre-lockdown. The highest TIRs was found within lockdown period. TAR decreased within time and TBR delivered similar results. Thus, same as in main analysis, sensitivity

analysis delivers data that has ascending TIR within lockdown – compared to the other two phases – and descending TBR and TAR. Schiaffini et al. underline our statement with their findings. They compared two phases and gained similar results (78).

In summary, both analyses deliver data that indicate that TIR phases ascend within time, and TBR and TAR phases descend. This assumption could be made and justified on less stress levels of individuals and a higher amount of time that enables to adopt a healthier lifestyle within pandemic.

4.4. Scan frequency

were evaluated based on total isCGM scan frequencies, and on mean daily isCGM scan frequencies. There is nearly no difference in the mean and also total isCGM scan frequency of the main analysis between the lockdown phase and pre-lockdown phase (814 vs. 817 / 8.8 vs. 9.1 scans/day). Pre-lockdown (same season) had higher scan frequencies in total and mean values (899.0 and 11.5 scans/day). This can be found in Table 10.

Similar findings can be found in sensitivity analysis. Nearly no difference in scan frequencies (both – total and mean) could be found between lockdown and pre-lockdown phase (816 vs. 810 / 8.9 vs. 9.2 scans/day) but pre-lockdown (same season) had higher values (800 / 11.6 scans/day) as Table 15 shows.

Concerning the scan frequencies, it can be summed up, that there were more frequent scans (both – total and mean) in the pre-lockdown phase same season. This could be explained with the less routine isCGMs at the time. Another aspect could be that this time period might have been more stressful for subjects. Normal business life was not at all interrupted in these days. It could be hypothesized that the subjects suffered from higher pressure and busier lifestyles and, thus, led unhealthier lives. Accordingly, this might have led to uncertainty about the own diabetes data and resulted in more frequent scans.

There is no doubt, that people living with T1D are at a higher risk at suffering from severe COVID-19 infection when being infected – especially if the diabetes is not adjusted properly. Li et al. made a meta-analysis concerning the association between DM and poor outcome in patients with COVID-19. They included 30 studies with 6452 individuals where

they came to the result that DM was associated with composite poor outcome, a higher mortality rate and severe COVID-19 disease progress (31).

Their findings might underline the statement, the current study seems to make. People living with T1D know about being part of the high-risk group when being infected with COVID-19. Thus, they improved their lifestyles to have better glycemic values. By following a more healthier lifestyle the scan frequencies decreases as a matter of being more sure in what they do and eat.

4.5. Main analysis vs. sensitivity analysis

With the current data in can be stated, that there is no difference between main analysis and sensitivity analysis, even if the main analysis includes only subjects with all three phases for whom baseline data is available. isCGM data suggest that mean glucose was highest in pre-lockdown (same season), CV was same for all periods in both analysis and GMI and MAGE were highest in pre-lockdown (same season) as well – in both analyses.

Time in different ranges delivered best data of TIR in all three phases, same as TBR and TAR were lowest in both analysis in all phases.

Regarding the scan frequencies, total and mean isCGM scan frequencies were highest in pre-lockdown (same season) in both analyses.

4.6. Studies that underline the current findings

Schiaffini et al. evaluated a group of 22 pre-school and school children with T1D that use a basis-bolus IQ. They wanted to evaluate the effectiveness of exclusive return to parental care. Similar to this study, they compared a pre-lockdown phase to a lockdown phase and came to the result, that TIR was improved while TAR was decreased within the lockdown phase. They explained their findings with a better full-time control by the parents. There might have been more frequent glycemic level controls, better insulin management and a more precise meal preparation (78). Same as the current study, stress reduction might also be a good explanation. Moreover, parents might have been afraid of a COVID-19 infection of their child dealing with T1D reasoned by the higher risk of a severe infection of a badly adjusted diabetes. Thus, they might have done their best – and also have had more time – to deal with their children's diabetes treatment.

Tornese et al. made another retrospective data analysis of individuals with T1D and compared three periods of time with each other (one period before SARS-CoV-2 outbreak, one period when movements were reduced and one period within the complete lockdown). They included data of 13 young adolescent individuals and found a higher TIR within the lockdown and during the phase where movements were reduced than during the period before the pandemic. Thus, also came to the result, that the restrictions due to COVID-19 pandemic did not worsen glycemic control in people living with T1D. The individuals of this study reported more indoor-practices and more regular physical activities during the lockdown phase. This again, promotes psychological wellbeing and reduces anxiety, improves the general mood and the quality of sleep. Furthermore, in case of those young adolescents, maybe also the parents have had higher control during lockdown or reduced movement phases (79).

Bonora et al. observed that glucose control improved in the first week of the lockdown. They found an increasing TIR and a reduction of average BG in a group of 33 adults with T1D. Same as in the current study, they gained better results within the lockdown and same as in the current study. They explained it by more time in general – which could be used to compose healthier meals, or in general, to follow a more regular and healthy lifestyle. Furthermore, it could also be a motivation to have good glycemic control in order to be aware of more severe COVID-19 complications if not achieved. They confirmed their hypothesis by a control group of patients who continued their work routine. This group did not show an improvement in their glycemic control (80).

4.7. Studies that disprove the current findings

The results of the current study are, however, in strong contrast to the results of Ghesquie` re et al. (81). This retrospective data analysis included 229 (phase 1 2019) and 222 (phase 2 2020) pregnant women within two phases and compared their data in the same manner as the current study. They came to the result, that diabetes control was lower during the COVID-19 pandemic compared to the period before. However, they did not impact follow-up and explained their results by modified dietary habits, less physical activity and anxiety during the pandemic (81). Furthermore, there must be considered that their participants all were pregnant women – in contrast to the current study.

4.8. The role of telemedicine

As with all social activities that were not of highly importance, all activities among people were restricted if not strictly necessary. Follow-up checks in people with chronic disease as T1D were reduced in order to avoid infection and to enlarge other capacities in hospitals, especially intensive care units (ICU).

Telemedicine offers a way which avoids physical proximity but to stay close to people living with T1D. Most of the data collected by CGM can be analyzed and discussed remotely to make a statement on glycemic control and improve as well. This was and still is commonly done in Italy but not yet legal in Austria. Telemedicine in the field of diabetes could definitively be integrated in a business-as usual care in T1D in the aftermath (80). In that field, telemedicine could give a better continuity of the healthcare assistance by a simplification of communication.

4.9. Answer of the study hypothesis

The current study confirms the current Zero-Hypothesis and rebuts the current Alternative-Hypothesis.

The COVID-19 pandemic does not negatively affect glycemic control in people with T1D due to reduction of outpatient clinic service and elevated stress levels. Further, the findings in this thesis underline that the indication that the opposite effects of COVID-19 happened. As the general population and among them people living with T1D, people experienced in most cases a reduction of stress levels that are accompanied by social, environmental and business-life, the COVID-19 pandemic might have had the consequence that patients had more time to keep their glucose level in range. Another big important factor might have been, that people living with diabetes (and among those also people living with T1D) were dealt as a high-risk group. This might have sensibilized people living with T1D in order to pay attention to good glucose values due to the fact that, according to the American Diabetes Association, people living with T1D are more likely to have severe complications when being infected with COVID-19 and any other virus. Furthermore, if diabetes is well-management also the risk of a severe infection decreases (51).

Further studies in that field are necessary to make a statement in closer detail on the effect of the COVID-19 pandemic on people living with T1D.

5. Conclusion

The findings of the current study do not confirm the idea that the COVID-19 pandemic negatively affected people living with T1D. When being infected, patients with DM did have a higher risk for severe and more serious infection. However, if not infected at all, T1D patients might have led a healthier lifestyle during the pandemic years than during their normal “business-as-usual” life. Especially for children and young adolescents, the fact that their parents stayed home and had them under a 24/7 supervision might have been a big benefit when talking about diabetes treatment. In contrast, this group (children and young adolescents) might not have had the proper amount of time for their diabetes treatment in their normal daily lives. Moreover, due to busy school and work life, diabetes management might not have been at their highest priority.

Furthermore, another important contributor for people living with T1D was the additional motivation to engage in more physical exercise. Since the COVID-19 pandemic came as a surprise and forced global society to eliminate any kind of social engagement, people suddenly had more time to engage in self-care and, thus, may have done more at-home exercise as compared to their prior “business-as-usual” lives. They went outside to socialize and, thus, did more walking and hiking. Those more frequent walks might have led to healthier lifestyles in general. In addition, due to the complete cancellation of all social events, the COVID-19 pandemic also led to enormous stress reduction. Therefore, and for future research, more analysis of the social effects of the pandemic is necessary. In the current analysis, no social effects were analyzed or regarded.

COVID-19 emerged in global society as a surprise. Although known as a disease, people could not have guessed the massive impact this global pandemic would have on everyone’s life. Overnight, all human contact was dangerous and completely forbidden for the better for a longer period. Due to the spontaneity of this very pandemic, schools, universities, companies, and medical institutions had to adapt their working policies and found online meetings via various platforms to be helpful. Years after the pandemic, many businesses still operate with online tools and have grown to appreciate their features. The technical world would not have grown at this speed if it were not out of need. Accordingly, COVID-19 helped society to travel into a modern and more digital world. As regards medical institutions, telemedicine was introduced. Italy (80), for instance, was one of the countries that made great use of this tool, however, it was not broadly used in Austria. In

the future, Telemedicine will and must be simplified and improved – especially in Austria. With telemedical treatment, even better glucose targets might have been reached. Same as in universities and companies, where online meetings turned out to be a commonly used method, telemedicine should become and stay a normal method in the field of medicine as well.

This thesis only dealt with the data that was gained regarding diabetes management. No psychological statement or condition was investigated. Even if the COVID-19 pandemic and its lockdowns might have resulted in better diabetes conditions, no statement of whether it has led to better psychological conditions than before the isolation can be made. To gain such results, further research must be conducted.

In my opinion, the pandemic and the accompanying restrictions might have shown several things in retrospect: Firstly, only one small virus could and still can change peoples' lives immediately. Those changes can have massive positive and negative impacts on people's physiological conditions. Secondly, the pandemic showed us how spontaneous and flexible people can be: Just over a short period the number of online and remote meetings and appointments increased massively. Thirdly, COVID-19 and its accompanying lockdowns gave society a break which may have led to healthier and more thoughtful lifestyles. Lastly, it needs to be highlighted that all the above can only be said in retrospect.

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Appendix

Sample-ID	Pre-lockdown (same season)	Pre-lockdown	Lockdown	Phases (n)	Baselines
1001	yes	no	no	1	yes
1003	yes	yes	yes	3	yes
1004	yes	yes	yes	3	yes
1006	yes	yes	yes	3	yes
1009	yes	yes	yes	3	yes
1014	no	yes	yes	2	yes
1015	no	yes	yes	2	yes
1019	yes	yes	yes	3	yes
1020	yes	yes	yes	3	yes
1028	yes	yes	yes	3	yes
1032	yes	yes	yes	3	yes
1033	yes	yes	yes	3	yes
1034	no	yes	yes	2	yes
1035	yes	yes	yes	3	yes
1036	yes	yes	yes	3	yes
1037	no	yes	yes	2	yes
1038	yes	yes	yes	3	yes
1040	yes	yes	yes	3	yes
1041	yes	yes	yes	3	yes
1044	no	yes	yes	2	yes
1047	no	yes	yes	2	yes
1048	yes	yes	yes	3	yes
1050	yes	yes	yes	3	yes
1051	yes	yes	yes	3	yes
1054	no	yes	yes	2	yes
1055	yes	yes	yes	3	yes
1056	yes	yes	yes	3	yes
1057	yes	yes	yes	3	yes
1059	yes	yes	yes	3	yes
1060	yes	yes	yes	3	yes

1061	yes	yes	yes	3	yes
1065	yes	yes	yes	3	yes
1070	yes	yes	yes	3	yes
1072	yes	yes	yes	3	yes
1073	yes	yes	yes	3	yes
1075	yes	yes	yes	3	yes
1076	yes	yes	yes	3	yes
1079	no	yes	yes	2	yes
1081	yes	yes	yes	3	yes
1085	yes	yes	yes	3	yes
1086	yes	yes	yes	3	yes
1087	yes	yes	yes	3	yes
1088	no	yes	yes	2	yes
1090	yes	yes	yes	3	yes
1093	yes	yes	yes	3	yes
1094	yes	yes	yes	3	yes
1095	yes	yes	yes	3	yes
1096	yes	yes	yes	3	yes
1097	yes	yes	yes	3	yes
1098	yes	yes	yes	3	yes
1100	yes	yes	yes	3	yes
1101	yes	yes	yes	3	yes
1103	no	yes	yes	2	yes
1104	yes	yes	yes	3	yes
1106	yes	yes	yes	3	yes
1107	yes	yes	yes	3	yes
1111	yes	yes	yes	3	yes
1113	yes	yes	no	2	yes
1114	yes	yes	yes	3	yes
1122	yes	yes	yes	3	yes
1123	yes	yes	yes	3	yes
1125	yes	yes	yes	3	yes
1127	no	yes	yes	2	yes
1130	yes	yes	yes	3	yes
1131	no	yes	yes	2	yes

1132	no	yes	yes	2	yes
1134	yes	yes	yes	3	yes
1135	no	yes	yes	2	yes
1137	yes	yes	yes	3	yes
1140	yes	yes	yes	3	yes
1143	yes	yes	yes	3	yes
1144	yes	yes	yes	3	yes
1145	no	yes	yes	2	yes
1146	yes	yes	yes	3	yes
1150	yes	yes	yes	3	yes
1153	yes	yes	yes	3	yes
1154	yes	yes	yes	3	yes
1158	yes	yes	yes	3	yes
1160	yes	yes	yes	3	yes
1163	yes	yes	yes	3	yes
1164	yes	no	yes	2	yes
1092					yes

Table 16 – Data availability(1)