GLYCEMIC CONTROL IN CHILDREN WITH TYPE 1 DIABETES DURING THE COVID-19 PANDEMIC

GLYCEMIC CONTROL IN CHILDREN WITH TYPE 1 DIABETES DURING THE COVID-19 PANDEMIC

By RAEESHA RAJAN, BHSc

A Thesis Submitted to the School of Graduate Studies in Partial Fulfilment of the Requirements for the Degree of Master of Science

McMaster University MASTER OF SCIENCE (2022) Hamilton, Ontario (Health Research Methodology)

TITLE: Glycemic control in Children with Type 1 Diabetes During the COVID-19 Pandemic

AUTHOR: Raeesha Rajan, BHSc. (McMaster University)

SUPERVISOR: Dr. M. Constantine Samaan.

NUMBER OF PAGES: x, 51

Lay Abstract

The COVID-19 pandemic restricted face-to-face healthcare-based interactions to limit the spread of the virus. These restrictions posed as a challenge for children and youth with type 1 diabetes mellitus (T1DM), who relied exclusively on in-person clinic visits as part of their care regimen pre-pandemic. In this retrospective study, we assessed the association of the first year of the COVID-19 pandemic with measures of glycemic control (HbA1c), diabetic ketoacidosis (DKA), hospitalization, hyperglycemia, and hypoglycemia, compared to two years pre-pandemic. We determined that children living with type 1 diabetes had no deterioration of glycemic control measures, apart from an increase in hyperglycemia, during the first 12 months of the pandemic. This study provides insights into health outcomes of children living with T1DM in the early stages of the pandemic and offers a roadmap to guide the further avenues of exploration needed to assess the full impact of the pandemic on this population.

Abstract

Background: Since March 2020, health systems around the world shifted to virtual care approaches as social distancing measures were recommended to stem the spread of SARS-COV-2, the virus responsible for the COVID-19 pandemic. For children and families living with type 1 diabetes, virtual consultations in pediatric diabetes care were rare prior to the pandemic but became the norm since the start of the pandemic. Data regarding glycemic outcomes and comorbidities in children living with type 1 diabetes mellitus (T1DM) during the pandemic are limited, and there is a need for these data to drive future care models design and delivery.

Aim & Methods: The aim of this project was to assess the association of the COVID-19 pandemic with measures of glycemic control (HbA1c), hyperglycemia, hypoglycemia, diabetic ketoacidosis (DKA) and hospitalization for the period spanning March 2020-2021 at McMaster Children's Hospital, a tertiary pediatric academic center in Hamilton, Ontario, Canada. Data from the onset of virtual care were compared with data from two years pre-pandemic.

Results: The COVID-19 pandemic was not associated with changes in HbA1c (MD -0.14, p=0.058), hospitalization (OR 0.57, p=0.068), or hypoglycemia (OR 1.11, p=0.484), but was significantly associated with the increase in reported hyperglycemia (OR 1.38, p=0.003) and reduction in DKA presentation (OR 0.30, p=0.009).

Conclusions: Glycemic control was stable during the early stages of the COVID-19 pandemic, when virtual and hybrid care models prevailed in diabetes care. These results suggest that patients and their families were able to adapt to the uncertain circumstances of the pandemic. Virtual consultations for pediatric diabetes did not hinder glycemic control, and likely aided in the maintenance of diabetes management. Longitudinal studies are necessary before virtual

consultations should be recommended to replace in-person clinic visits, but the initial data seem encouraging.

Acknowledgments

The completion of this thesis could not have been possible without the contribution and support of several individuals. Thank you to my research supervisor, Dr. M. Constantine Samaan, for your constant mentorship throughout this project and over the past few years. The time and dedication you have for your students is unmatched, and it was truly a privilege to learn under your guidance. Our meetings quickly became something I look forward to each week, as I was eager to hear the clinical, research, and general life advice you had to impart. Thank you for your encouragement through the difficult obstacles that this process presented, and for helping me grow in confidence and curiosity.

Thank you, Dr. Uma Athale and Dr. Lehana Thabane, for being a part of my research committee. Your feedback and encouragement throughout this process was invaluable to the project. It has been a privilege to learn from you both.

Thank you, Dr. Rod Rassekh, for being my external committee member. I appreciate you taking the time to review my thesis project and provide me with feedback.

Thank you to my family, friends, and peers for your unwavering support throughout my masters. Thank you for constantly checking in on me and getting me through the tough obstacles I faced. Thank you for also celebrating every milestone with me, no matter the size. I am grateful to be surrounded by individuals who are so driven by the work they do, and for inspiring me to do the same.

Table of Contents

List of Abbreviations and Symbols

T1DM = Type 1 Diabetes Mellitus

HbA1c = Glycosylated Hemoglobin A1c

MDI = Multiple Daily Injections

CGM = Continuous Glucose monitor

COVID-19 = Coronavirus-19

CGC Study = COVID-19 and Childhood Diabetes Study

HiREB = Hamilton Integrated Research Ethics Board

GEE = Generalized Estimating Equations

MD = Mean Difference

OR = Odds Ratio

95% CI = 95% Confidence Interval

MI = Multiple Imputations

List of Figures and Tables

Declaration of Academic Achievement

I hereby certify that I am the sole author of this thesis and declare that this thesis consists of original work of which I have authored. This is a true copy of the thesis, including any required final revisions as accepted by my examiners.

I acknowledge the work of two undergraduate thesis students, Amandeep Saini, and Claudia Cargnelli, for their contributions in extracting patient data to build the database from which this study and analyses were conducted.

I have used standard referencing practices to acknowledge ideas, research techniques and other materials that belong to others. Furthermore, I hereby certify that I am the sole source of the creative works and/or inventive knowledge described in this thesis.

____ Raeesha Rajan

Chapter 1

1.1 Pediatric Type 1 Diabetes

Type 1 Diabetes mellitus (T1DM) is the most common endocrine disorder in children and youth worldwide, with over 1.1 million cases of children worldwide.[1,2] Although T1DM can occur at any age, teenage diagnosis with T1DM of around 13-14 years represent a specific challenge with managing this age group due to the complex biopsychosocial variables in this vulnerable stage in life.[3-5] T1DM is characterized by the body's inability to produce insulin due to the autoimmune destruction of the beta cells in the pancreas. The lack of insulin causes hyperglycemia and impaired glucose utilization, which in turn results in the breakdown of muscle and fat energy stores to provide energy for the body. Fat breakdown for extended periods produces ketones, which causes acidosis and sometimes a significant, life-threatening condition known as diabetic ketoacidosis (DKA). Diabetes can be associated with multiple complications especially when not fully managed including nephropathy, retinopathy, and neuropathy.[3-5]

There is a strong genetic component in the etiology of T1DM. The risk of developing T1DM with no family history is approximately 0.4%, while this risk rises up to 25% if both biological parents have this condition.[3,6] There is some evidence that environmental factors may trigger the onset of T1DM in children who are genetically predisposed, such as persistent or recurrent enteroviral infection, frequent respiratory or enteric infections, poor hygiene and living conditions, weight gain, poor diet, psychological stress and steroid treatment.[3,7,8]

While initial presentations of T1DM vary between patients, most commonly children have symptomatic hyperglycemia with or without acidosis, with polydipsia, polyuria, polyphagia, weight loss, and nocturia. Symptoms of feeling unwell such as fatigue, weakness, candida rashes, blurry vision, nausea, and vomiting may also be present initially.[3-5] Diabetes diagnosis is most often confirmed by the presence of classic symptoms and testing of fasting or random plasma glucose levels supported by glycosylated hemoglobin A1c (HbA1c) levels. Guidelines define diabetes as having a random plasma glucose ≥ 11.1 mmol/L (≥ 200 mg/dL) or fasting plasma glucose ≥ 7.0 mmol/L (≥ 126 mg/dL), where fasting is defined as no caloric intake for 8 hours.[3-5] A positive test for autoantibodies against pancreatic islet cells proteins, including glutamic acid decarboxylase, insulin, insulinoma-associated protein, and zinc transporter ZnT8, while not needed clinically to confirm the diagnosis, can support it.[3-5]

Due to the complex nature of the disease, treatment plans include insulin therapy as the main intervention.[3-5] These treatment plans are devised by an interdisciplinary healthcare team including pediatric endocrinologists, nurses, dieticians, social workers, and child life specialists. Insulin is the cornerstone of management of T1DM, and is primarily delivered via daily injections or insulin pump therapy.[4,5,9] Insulin dosage and regimens are devised alongside meal plans, which are often developed with the child and family's usual eating patterns and carbohydrate intake and daily physical activity in mind. Patients and their families are taught how to count carbohydrates in food, and to measure and respond to glucose levels in order to consistently uphold targets and avoid excursions.[4,5,9] Additionally, patients and their families are provided with psychosocial support and monitoring of diabetes management burnout and conditions such as depression, anxiety and eating disorders.[4,5,9] Such conditions are common among children living with diabetes as a result of multiple factors including body image disturbance.[10,11] Psychosocial problems can also cause and result from poor glycemic control by affecting children's ability to adhere to their dietary and medication regimens.[4,5,9,10]

Depending on the age of the child, heavy parental involvement in upholding treatment regimens may be required in the first few years of diagnosis, along with support by the healthcare system in schools.[4,5,9] As such, following the patient and their family to ensure adequate transitioning and sharing of responsibility is crucial to upholding diabetes management, and avoid adverse events and potential acute or chronic complications.[4,5,9,12]

National and international guidelines recommend that patients and their families meet with the interdisciplinary diabetes care team regularly to assess for glycemic control, growth, treatment plan and adherence, and provide the necessary treatment adjustments.[4,5,9] Diet and physical activity are also assessed, to ensure insulin regimens are adequately meeting patients' needs. A HbA1c target level of <7% is considered optimal for most children with T1DM, with increasing levels associated with high risk of adverse events and diabetes-related complications.[4,5,9] Yearly routine screening is also conducted to assess for complications and other autoimmune disorders such as celiac disease and hypothyroidism.[4,5,9] It is evident that diabetes management is complex with a need of constant consideration for multiple aspects of wellbeing. As such, the involvement of the diabetes care team is integral to a successful adoption of a treatment plan that meets the needs of the patient and maintain health outcomes.[4,5,9]

1.2 The Role of Technology in Diabetes Care

The use of technology in health services such as education, counselling, communication, and management, has been identified as a global priority in recent years. Young people have embraced technology and incorporated it into their daily lives even further as the pandemic unfolded. For example, for children aged 6-12, screen time in 2020 increased from 2.6 hours/day to 5.9 hours/day in Ontario alone.[13] The Canadian Internet Use Survey from 2020 found that 98% of Canadian households with children ages <18 had access to and regularly used the internet.[14] As such, this generation may be able to use technology to support their health needs. Technology in healthcare also has the potential to facilitate parts of complex treatment regimen through processes as simple as reminders for patients to adhere to their treatment plans using devices that highlight treatment tasks with greater precision and efficiency, such as insulin pumps and glucose sensors.[15,16] These devices also tend to be equipped with advanced data capturing and sharing capabilities, which allows the tracking and evaluation of health data. [15-18] Telehealth can also facilitate on-demand support for patients through communications via e-mail, phone, or video conferencing.[17,18] This is of particular benefit for patients who live in remote locations, for whom regular in-person clinic visits may not be readily accessible.[17,19,20]

The field of diabetes management has seen impressive innovation in technology that facilitates the complex treatment regimens.[20-22] Today, children with diabetes have access to insulin pumps and continuous glucose monitoring systems (CGM).[22-25] Increasingly, these devices can be paired in a pump-based closed-loop system to allow for the insulin dosages to be regulated in response to glucose levels.[20,23] These devices have been successful in maintaining target glycemic levels and reducing the number of adverse events.[23-26] Prior to the COVID-19 pandemic, patients and families also had access to their diabetes care team via phone or e-mail communications. These communications provided patients and their families the opportunity to seek additional support in diabetes management.[15,16] Such tools include mobile applications or internet-based platforms that encourage adherence to diabetes management routines with reminders, motivational messaging, and education, as well as facilitate interactions with healthcare providers virtually.[15-17] Some tools have even incorporated features found in social media, such as the ability to interact with other diabetes patients,[27] and have gamified learning about diabetes management.[28] These interventions have shown great promise in maintaining or improving glycemic control and attitudes towards diabetes management in children with T1DM and their families, particularly for those with suboptimal glycemic control.[15,16]

1.3 The COVID-19 Pandemic

The SARS-CoV-2 virus, the causative agent of COVID-19, was declared a global pandemic by the World Health Organization on March 11th, 2020.[29] In Ontario, this designation was quickly followed by isolation and distancing measures to slow the spread of the virus.[30] Patients who relied on outpatient services, including pediatric diabetes care, were no longer seen in clinic to preserve hospital services for those who required emergency support from contracting the COVID-19 virus and prevent the spread of the virus. The pandemic led to delays in seeking care, more severe initial presentation of newly diagnosed children with diabetes with more DKA and more severe DKA along with mental health concerns.[31-34] While shortage of diabetes supplies was not a major problem faced by pediatric diabetes patients in Canada, this was observed in some parts of the world.[35]

To tackle the cancellation of in-person clinic visits, virtual consultations were adopted. Prior to the pandemic, the healthcare system utilized video-based technology in less than 0.5% of instances of care delivery in North America.[36,37] During the first wave of the pandemic spanning about 5 months, and in subsequent waves, many outpatient services utilized a completely virtual consultation system.[38,39] While infrastructure to conduct virtual visits was quickly implemented, this switch was very novel for the system as a whole. Important aspects of in-person clinic visits, such as bloodwork and taking anthropometric measures, could not be conducted virtually. Other challenges that arose for patients, particularly for those with lower socio-economic stability or living in rural areas, were limits with access to technological devices and internet connection, and a private setting to conduct virtual visits.[19] Despite these challenges, virtual consultations aimed to maintain care, with options for patients and their families to continue to discuss diabetes management strategies and get the support they need to control diabetes.[40-42]

An overall decrease in physical activity was noted across many patients due to the cancellation of organized activity and virtual schooling.[43-46] As such, virtual consultations were crucial during this time in adjusting diabetes management plans.

1.4 Gaps in the Literature

With the rapid pivot to a virtual and hybrid delivery of healthcare with the COVID-19 pandemic, it is unclear how the pandemic has impacted glycemic control in children with diabetes globally. The advantages and disadvantages of virtual care will no doubt be debated over the coming years. The potential benefits cited include convenience, cost-effectiveness, and ease of access to care; potential disadvantages include accessibility barriers and inability to obtain reliable clinical measurements such as anthropometrics and blood tests.[40,41,47] These decisions must factor in implications at the system, provider, and patient/family levels.[41,42] It is likely that hybrid models of care are here to stay, and the format that they will be delivered through remains a work in progress.[48]

Evidence continues to emerge on the impact of the COVID-19 pandemic on various pediatric patients living with diabetes.[49,50] A meta-analysis of observational studies of patients with diabetes reported no significant change in HbA1c after the COVID-19 lockdown.[51] Pediatric-specific studies reported similar results in Italy, Germany, the United States, and Canada.[43,49,50,52] However, studies reporting on patients from countries such as India, impacted by diabetes treatment supply shortages and having less access to virtual consultation platforms, reported worsening glycemic control.[35]

This thesis project was designed to assess the impact of the COVID-19 pandemic on health outcomes in children living with T1DM at McMaster Children's Hospital, a tertiary pediatric academic center in Hamilton, Ontario, Canada. At the hospital, clinical care moved to almost complete virtual care from March-September 2020. Then, limited hybrid care was offered October-December 2020. From January-March 2021, care returned to virtual platforms due to the new wave of the pandemic. Then, hybrid care continued to be the current norm. These hybrid models of care are novel, and an assessment of how glycemic control has changed with using them is a crucial question to answer to inform the next phases of care and to drive policy decisions about resource allocation.

1.5 Research Questions and Methods

Main outcome: In children with T1DM, has there been a change in glycemic control before and during COVID-19 pandemic?

Other outcomes: How does the COVID-19 pandemic impact diabetes-related morbidities?

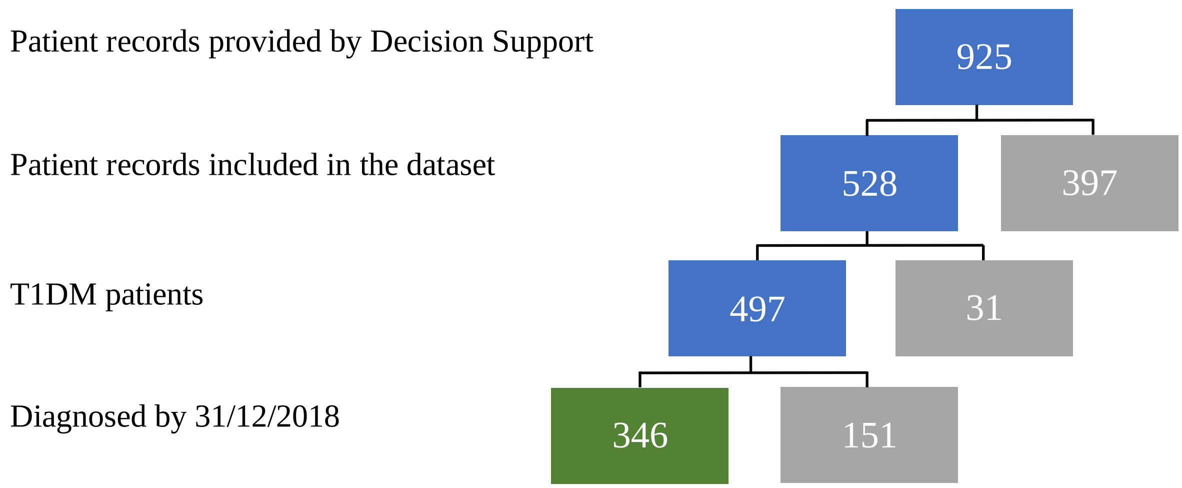
The main objective of this study was to determine the changes in glycemic control, measured by HbA1c, during the pandemic. We hypothesized that glycemic control would deteriorate during the pandemic with virtual or hybrid care models when compared to the pre-pandemic face-to-face care models.

The secondary objective was to determine changes in diabetes-related morbidities (i.e., DKA, hospitalization, hypoglycemia, and hyperglycemia,) during the pandemic when compared to the pre-pandemic phase, where available. We hypothesized that diabetes-related morbidities will increase during the pandemic.

The data utilized in this study were obtained from the COVID-19 and Childhood Diabetes (CGC) Study and did set up time timeline for the study to include data from two years pre-pandemic and the first year of the pandemic. A summary of the selection process is presented in Figure 1. The decision support team provided a secure list of 925 medical record numbers of patients who were enrolled in the Diabetes Program at McMaster Children's Hospital up to May 18, 2021. Of these, 397 patients did not meet our inclusion criteria of age range, date of diagnosis, or follow-up time with our diabetes clinic.

Of the 528 patients from whom we do have extracted data, only 497 were T1DM patients. Of these patients, 346 were diagnosed by the end of 2018, and had adequate data for comparison of pre-pandemic data with pandemic data. As a result, 346 patients were included in the present study.

Figure 1. Selection Process for Included Patients



For the CGC study dataset, all data from registered nurse, nurse practitioner, registered dietician, social worker, and child life specialist notes were extracted. Only the data relevant to the research questions were analyzed further in the present study. These include age at diagnosis, diabetes duration, sex, gender, visit date, glycosylated hemoglobin A1c (HbA1c) values, dates of data collection, treatments including multiple daily injections (MDI) or insulin pump therapy data, continuous glucose monitor (CGM) use, diabetic ketoacidosis (DKA), hospitalizations, hypoglycemic events, hyperglycemic episodes, weight, weight percentile, height, height percentile and Body Mass Index (BMI) z-score.

1.6 Research Ethics Approvals

This retrospective chart review involved reviewing and extracting data from the electronic medical records of children and adolescents with T1DM followed at the Pediatric Diabetes Program at McMaster Children's Hospital in Hamilton, Ontario. This study was approved by the Hamilton Integrated Research Ethics Board (HiREB) for an exemption of informed consent due to the anonymous nature of information and the use of aggregate data that are included in the dataset. The study was performed in accordance with the guidelines of the Tri-Council Policy Statement 2 (TCPS2) and the principles of Good Clinical Practice. Data confidentiality and patient anonymity were maintained at all times.

Chapter 2

Assessment of the impact of the COVID-19 pandemic on outcomes in pediatric patients with type 1 diabetes mellitus: A single center study

Raeesha Rajan[1,2,3], Uma Athale[1,4], Joycelyne Efua Ewusie[5], Karen McAssey[1,2], Lehana Thabane[3,5,6,7], M Constantine Samaan[1,2,3*]

[1]Department of Pediatrics, McMaster University, Hamilton, Ontario, Canada

[2]Division of Pediatric Endocrinology, McMaster Children's Hospital, Hamilton, Ontario, Canada

[3]Department of Health Research Methodology, Evidence and Impact, McMaster University, Hamilton, Ontario, Canada

[4]Division of Hematology Oncology, McMaster Children's Hospital, Hamilton, Ontario, Canada

[5]The Research Institute Biostatistics Unit, St Joseph's Healthcare Hamilton, Hamilton, Ontario, Canada

[6]Department of Anesthesia, McMaster University, Hamilton, Ontario, Canada

[7]Centre for Evaluation of Medicines, Hamilton, Ontario, Canada

*Corresponding Author: Dr. M. Constantine Samaan

Department of Pediatrics,

McMaster University,

Division of Pediatric Endocrinology,

McMaster Children's Hospital,

1280 Main Street West, 3A-57,

Hamilton, Ontario L8S 4K1

Tel: 001-905-521-2100, ext. 75926

Fax: 001-905-308-7548

E-mail: samaanc@mcmaster.ca

ABSTRACT

Background: The COVID-19 pandemic led to a significant shift pediatric diabetes care delivery with emerging virtual and hybrid care models. It is unclear if these models have impacted patient outcomes, and whether virtual care is a sustainable approach for care delivery in this patient population.

Objectives: The main objectives of this study were to assess glycemic control and diabetes-related outcomes in children living with Type 1 Diabetes Mellitus (T1DM) during the COVID-19 pandemic at a tertiary pediatric academic center in Canada.

Subjects: Patients with a diagnosis of T1DM for at least one year and cared for within the Pediatric Diabetes Program at McMaster Children's Hospital were included.

Methods: In this retrospective chart review, we compared data for glycemic control using glycosylated hemoglobin A1c (HbA1c) and other outcomes including changes in diabetic ketoacidosis (DKA), hospitalizations, hypoglycemia and hyperglycemia using data from two years before and during the first year of the pandemic. We utilized generalized estimating equations (GEE) to model potential influencers of HbA1c during the pandemic.

Results: There were 346 eligible patients for inclusion in the analysis. While HbA1c remained stable during the pandemic when compared to the pre-pandemic phase (MD -0.14, p=0.058), more newly diagnose patients presented in DKA (X^2 =12.94, p<0.001) and required hospitalization (X^2 =50.94, p<0.001). In those with established diabetes, the pandemic phase was characterized by an increase in reported hyperglycemia (OR 1.38, p=0.003) and reduced DKA (OR 0.30, p=0.009), while hospitalization rates (OR 0.57, p=0.068) and hypoglycemia (OR 1.11, p=0.484) were comparable to the pre-pandemic phase.

Conclusions: Virtual and hybrid T1DM care models during the COVID-19 pandemic were successful in maintaining glycemic control. However, there was a significant burden of diabetes-related comorbidities in this population. Further studies are needed to optimize care delivery to lower glucose variability and DKA and personalize the choice of virtual care for patients.

Keywords: Type 1 diabetes, children, COVID-19, glycemic control

INTRODUCTION

In March 2020, the World Health Organization declared COVID-19 a global pandemic.[1,2] This pandemic, caused by the then novel SARS-CoV-2 virus, led to global lockdowns and the implementation of social distancing measures to curb viral spread and prevent healthcare systems from being overwhelmed.[3-5] For most children, schools and organized activities were moved to virtual platforms whenever possible.[6,7] The ongoing waves of the virus variants continue to impact access to healthcare services, resumption of in-person schooling, work, and social activities that will likely continue into the foreseeable future.[6,8]

Type 1 diabetes mellitus (T1DM) is the most common pediatric endocrinopathy with almost 1.1 million cases globally.[9,10] During the pandemic, healthcare systems re-directed finite healthcare resources to the pandemic response; pediatric outpatient services for chronic illnesses such as diabetes pivoted to virtual care models including video or telephone consultations.[8,11-13] Even as COVID-19 vaccinations were up-scaled, non-urgent in-person clinical services continued to be disrupted.[12,14]

While similar approaches to virtual care were adopted across pediatric diabetes clinics internationally, there were significant uncertainties regarding their efficacy when deployed on such a global scale.[11,15-20]

Over the past few decades, T1DM patients increasingly relied on technology including insulin pumps and continuous glucose sensors as part of their diabetes management – trends that continue to revolutionize care in this population.[11,17,21,22]

In the pre-pandemic phase, in-person visits were the norm to provide diabetes care in Canada[23-25], and virtual consultations occurred in <0.5% of clinic visits.[26,27] The overnight pivot to virtual care demonstrated a degree of resilience in care delivery to support patient care and maintain outcomes during the pandemic.[11,17]

Even before the pandemic, virtual care was reported to keep patients engaged in their diabetes management, improve treatment adherence, was feasible and cost-effective. This care modality was also acceptable to patients and families.[17,28-31] Initial indicators from studies conducted prior to the pandemic favored virtual care in remote communities.[21,31,32] Emerging evidence of virtual care during COVID-19 suggest inconsistent results of its impact on diabetes care.[16,33] Currently, only short-term data that report on specific patient populations have become recently available, and this approach limits the generalizability of study findings to all pediatric diabetes patients.

The aim of the study was to compare T1DM outcomes before and during the COVID-19 pandemic including glycemic control, diabetic ketoacidosis (DKA), hospitalizations, hypoglycemia, hyperglycemia. We tested the hypothesis that in children with T1DM, glycemic control and diabetes-related morbidities will worsen during the pandemic when compared to the pre-pandemic phase.

METHODS

This study is a retrospective chart review from the COVID-19 Effects on Glycemic Control in Children Living with Diabetes (CGC) Study.

We included boys and girls aged 2-18 years with a diagnosis of T1DM for at least one year and attended the Pediatric Diabetes Program at McMaster Children's Hospital, a tertiary pediatric academic center in Ontario, Canada.

The study included patients diagnosed by the end of 2018 and had longitudinal follow-up data. We included those patients with a confirmed diagnosis of T1DM based on standard criteria for at least one year to rule out other forms of diabetes.[24,25,34] We excluded patients with cystic fibrosis-related diabetes, monogenic diabetes, steroid-induced hyperglycemia, and type 2 diabetes. Patients less than 2 years of age were also excluded to avoid the potential inclusion of neonatal and genetic forms of diabetes.

We collected data for the two years pre-pandemic (March 15, 2018-March 14, 2020), and for one year during the pandemic (March 15, 2020-March 14, 2021). During the pandemic period, clinical care was almost completely virtual from March-September 2020. Then, limited hybrid care occurred from October-December 2020, where some in-person care resumed. From January-March 2021, care returned to virtual platforms due to the new wave of the pandemic. The data from the pandemic phase, especially HbA1c, were limited by restrictions of patient access to laboratory and clinic point-of -care testing, so we included patients who had at least one HbA1c during the first year of the pandemic. We collected data including the age at diagnosis, diabetes duration, sex, visit date, glycosylated hemoglobin A1c (HbA1c), treatments including Multiple Daily Injections (MDI) or insulin pump therapy data, continuous glucose monitor (CGM) use, DKA, hospitalizations for diabetes-related causes, hypoglycemic events, and hyperglycemia.

We also collected available anthropometric data including weight, weight percentile, height, height percentile, and Body Mass Index (BMI) z-score.[35] Of note, the number of patients who had data on height measured at the hospital during the pandemic was relatively small (n=110, 31.80%), and weights included a mix of home-reported (n=189, 61.00%) and hospital-measured (n=122, 39.00%) data. We included BMI z-score data on a subset of patients who had weights and heights measured in the clinic.

For the HbA1c analysis, we compared the pre-pandemic phase data when patients exclusively had in-person clinic visits, to the pandemic phase, when clinics were conducted using a virtual or hybrid care model with some patients receiving virtual care and others in-person care.

The main outcome of the study was the comparison of the change in HbA1c during the pandemic when compared to the pre-pandemic phase. Other outcomes analyzed included DKA and hospitalizations at diagnosis and in those with established diabetes. In addition, data on hypoglycemia and hyperglycemia that were reported or documented via CGM, glucometer, or logbook reviews were included.

DKA was defined as hyperglycaemia with blood glucose >11.00 mmol/L (200mg/dL), venous blood gas-based pH <7.30, serum bicarbonate <15 mmol/L and the presence of ketones (ß-hydroxybutyrate ≥3mmol/L in blood, moderate-large ketonuria).[34,36] Hospitalizations refer to diabetes-related reported emergency department visits or overnight hospital admissions. Hypoglycemia was defined as a plasma glucose level ≤3.9 mmol/L (70 mg/dL) and hyperglycemia was defined as a plasma glucose level ≥13.3 mmol/L (240 mg/dL).[34,36]

The Hamilton Integrated Research Ethics Board approved a waiver of consent due to the anonymous and aggregate nature of data used in the analyses. The study was performed in accordance with the guidelines of the Tri-Council Policy Statement 2 and the basic principles of Good Clinical Practice. Data confidentiality and patient anonymity were maintained at all times.

Statistical Analysis

Continuous variables were presented as a mean (SD) with range where indicated, and dichotomous variables were reported as number (%). Tests for multicollinearity were conducted to ensure predictors used in the model were not highly correlated with one another. A variance inflation factor <5 was used to meet this assumption.[37]

We utilized the paired t-test for comparisons of continuous variables and McNemar's test for binary variables to report differences in repeated measures pre-pandemic when compared to the pandemic phase. To assess differences in the proportions of patients diagnosed pre-pandemic to those diagnosed during the pandemic and their clinical presentations, we utilized the Wald Chi-Squared test.

The generalized estimating equation (GEE) model was applied to compare HbA1c levels before and during the pandemic and was adjusted for age, sex, treatment type, sensor use, weight and diabetes-related morbidities.[38] [23,25,39] GEE models were also used to assess change in hypoglycemia, hyperglycemia, DKA, and hospitalizations.[38] These models were adjusted for age, sex, treatment type, and sensor use.[38,40] For this analysis, we utilized the first-order auto-regressive working correlation matrix that recognizes correlations are highest between adjacent times and systematically decrease with increasing distance between time points.[38,40]

Continuous variables were reported using mean difference (MD) with a 95% confidence interval (CI) and binary variables were presented as an odds ratio (OR) with a 95% CI.

To assess the robustness of the findings, we utilized a sensitivity analysis that assessed the impact of missing data.[41,42] We used the multiple imputations (MI) approach to address missing data, reported as a number and percent, and re-ran the GEE model for outcomes as a sensitivity analysis. The data analyses were performed using SPSS 28.0.[43]. Significant was set at alpha<0.05.

Table 1. Characteristics of Study Participants

	Pre-pandemic		Pandemic	P-value
	2018	**2019**	**2020**	
Total Patients, *n*	346	-	-	
Newly Diagnosed, *n*	58	55	81	<0.001[+]
Sex, *n* (%)				
Male	187 (53.90)	-	-	
Female	159 (46.10)	-	-	
Age at study inclusion, mean (SD), years				
Total	10.30 (3.50)	-	-	
MDI, Male	10.40 (3.70)	-	-	
MDI, Female	10.90 (3.30)	-	-	
Pump, Male	10.10 (3.60)	-	-	
Pump, Female	10.10 (3.30)	-	-	
Diabetes duration, mean (SD), years				
Total	4.50 (3.30)	-	-	
MDI, Male	4.60 (3.90)	-	-	
MDI, Female	4.00 (3.10)	-	-	
Pump, Male	4.50 (3.30)	-	-	
Pump, Female	4.60 (3.20)	-	-	
Treatment, *n* (%)				0.317
MDI	187 (54.00)	142 (41.00)	139 (40.20)	
Pump	159 (46.00)	204 (59.00)	207 (59.80)	
CGM Use, *n* (%)	**n=309**	**n=331**	**n=338**	<0.001
	136 (44.00)	168 (50.80)	205 (60.70)	
Weight, mean (SD), kg	**n=333**	**n=345**	**n=122**	
Total	43.50 (17.50)	48.10 (18.70)	53.28 (18.40)	
MDI, Male	41.20 (18.20)	47.90(19.20)	56.50 (19.20)	
MDI, Female	41.60 (15.60)	48.00 (18.60)	46.00 (16.40)	
Pump, Male	46.40 (17.20)	48.90 (19.30)	55.10 (18.90)	
Pump, Female	45.00 (18.00)	47.60 (17.50)	52.50 (17.80)	
Weight %ile, mean (SD)	**n=333**	**n=345**	**n=122**	

Total	66.80 (25.70)	69.00 (25.30)	70.40 (25.20)	0.024++
MDI, Male	67.75 (27.41)	66.14 (29.70)	73.80 (28.10)	
MDI, Female	63.83 (24.44)	68.15 (24.00)	57.80 (24.20)	
Pump, Male	67.04 (25.44)	70.10 (24.80)	70.60 (25.50)	
Pump, Female	68.62 (24.17)	71.02 (22.30)	73.20 (21.60)	
Height, mean (SD), cm	**n=333**	**n=344**	**n=110**	
Total	145.70 (21.70)	150.30 (21.20)	155.40 (21.50)	
MDI, Male	142.50 (24.60)	150.50 (23.20)	155.40 (28.50)	
MDI, Female	143.40 (19.80)	147.70 (19.90)	148.90 (18.70)	
Pump, Male	150.90 (20.90)	152.50 (22.70)	160.40 (19.20)	
Pump, Female	147.70 (18.00)	150.00 (17.70)	153.70 (16.50)	
Height %ile, mean (SD)	**n=333**	**n=344**	**n=110**	
Total	59.70 (28.10)	60.90 (28.30)	62.00 (27.80)	0.383++
MDI, Male	58.70 (29.20)	58.00 (29.60)	63.10 (26.40)	
MDI, Female	56.30 (27.80)	55.90 (28.00)	49.30 (30.70)	
Pump, Male	59.70 (27.80)	62.90 (28.90)	64.70 (28.70)	
Pump, Female	65.10 (26.20)	65.30 (25.80)	64.70 (25.70)	
BMI Z-score, mean (SD)	**n=333**	**n=344**	**n=110**	
Total	0.70 (1.20)	0.70 (1.00)	0.80 (1.10)	0.004++
MDI, Male	0.80 (1.30)	0.80 (1.10)	1.00 (1.20)	
MDI, Female	0.60 (0.80)	0.80 (0.90)	0.50 (1.00)	
Pump, Male	0.70 (1.40)	0.80 (1.00)	0.80 (1.00)	
Pump, Female	0.60 (1.10)	0.70 (0.90)	0.90 (1.00)	

Total number of participants reported per outcome is bolded and specified by n.

Abbreviations: SD = standard deviation, MDI = multiple daily injections, *n*= number of participants, CGM = continuous glucose monitor, kg = kilograms, cm = centimeters, BMI = Body Mass Index.

P-values compared differences in characteristics pre-pandemic to pandemic phases and were obtained from McNemar's tests unless otherwise indicated.

\+ P-values from Wald chi-squared tests.

++ P-values from paired t-tests.

Table 2. Glycemic Outcomes of Study Participants

	Pre-pandemic		**Pandemic**	**P-value**
	2018	**2019**	**2020**	
HbA1c, mean (SD) %	**n=337**	**n=345**	**n=344**	
Total	8.10 (1.60)	8.20 (1.50)	8.40 (1.50)	0.076++
MDI, Male	8.40 (1.70)	8.40 (1.80)	8.80 (1.80)	
MDI, Female	8.40 (1.90)	8.60 (1.90)	8.90 (1.80)	
Pump, Male	8.00 (1.20)	8.10 (1.20)	8.10 (1.10)	
Pump, Female	7.70 (1.00)	7.80 (1.00)	8.00 (1.10)	
Hypoglycemia, n (%)	**n=335**	**n=341**	**n=341**	
Total	323 (96.40)	332 (97.40)	330 (96.80)	0.819
MDI, Male	68 (21.10)	69 (20.80)	68 (20.60)	
MDI, Female	54 (16.70)	59 (17.80)	59 (17.90)	
Pump, Male	110 (34.10)	111 (33.40)	111 (33.60)	
Pump, Female	91 (28.20)	93 (28.00)	92 (27.90)	
Hyperglycemia, n (%)	**n=332**	**n=338**	**n=339**	
Total	278 (83.70)	277 (82.00)	301 (88.80)	0.011
MDI, Male	56 (20.10)	55 (19.90)	59 (19.60)	
MDI, Female	44 (15.80)	45 (16.20)	56 (18.60)	
Pump, Male	95 (34.20)	97 (35.00)	104 (34.60)	
Pump, Female	83 (29.90)	80 (28.90)	82 (27.20)	
DKA				
DKA at diagnosis**,** n (%)	22 (37.90)	23 (41.80)	36 (44.40)	<0.001+
DKA with established diabetes, n (%)	19 (5.50)	20 (5.80)	12 (2.90)	<0.001
MDI, Male	5 (26.30)	8 (40.00)	2 (16.70)	
MDI, Female	7 (36.80)	4 (20.00)	4 (33.30)	
Pump, Male	5 (26.30)	6 (30.00)	4 (33.30)	
Pump, Female	2 (10.50)	2 (10.00)	2 (16.70)	
Hospitalization				
Hospitalization at diagnosis, n (%)	51 (87.90)	52 (94.50)	77 (95.10)	<0.001+
Hospitalization with established diabetes, n (%)	31 (9.00)	34 (9.80)	26 (7.50)	<0.001
MDI, Male	9 (29.00)	9 (26.50)	4 (15.40)	
MDI, Female	11 (35.50)	8 (23.50)	8 (30.80)	
Pump, Male	7 (22.60)	13 (38.20)	7 (26.90)	
Pump, Female	4 (12.90)	4 (11.80)	7 (26.90)	

Total number of participants with available reported data per outcome is bolded and specified by n.
Abbreviations: SD = standard deviation, MDI = multiple daily injections, *n*= number of participants, HbA1c = glycosylated hemoglobin A1C, DKA = diabetic ketoacidosis.
P-values compared differences in characteristics pre-pandemic to pandemic phases and were obtained from McNemar's tests unless otherwise indicated.
+ P-values from Wald chi-squared tests.
++ P-values from paired t-tests.

RESULTS

Participants' characteristics are reported in Table 1. We included 346 patients who met the inclusion criteria. Mean age at study inclusion was 10.30 ± 3.50 years (range from 2.00-16.20 years) at inclusion. Participants had diabetes for 4.50 ± 3.30 years (range from 1.00-15.70 years) at inclusion.

There were 159 (46.10%) female participants, and puberty and menarche data were not available. There was a significant increase in the number of newly diagnosed patients during the first year of the pandemic, when compared to the two years in the pre-pandemic phase ($X^2 = 16.52$, $p<0.001$).

The number of patients using insulin pump therapy increased over time compared to MDI treatment regimen and was stable during the pandemic as pump initiation activities slowed down with lockdowns (pump use pre-pandemic 2018: 46.00%, 2019: 59.00%; pandemic: 59.80%; p=0.137). The use of CGM increased over time and climbed further during the pandemic (pre-pandemic 2018: 44.00%, 2019: 50.80%; pandemic: 60.70%; p<0.001).

An important trend for the rise in BMI z-score was noted in the subset of data available for analysis (n=110, t=-2.97; 95% CI -0.22,-0.04, p=0.004). While this data set is smaller than the full study population owing to the lack of hospital-based height data measures, the elevation in BMI z-score was driven by the weight percentile rise during the pandemic (n=122, t=-2.28; 95% CI -4.16,-0.29, p=0.024). In an exploratory sex-based analysis for BMI Z-score, females had a more significant rise in BMI z-score than males (Males n=62, t=-1.86, p=0.068; Females n=48, t=-2.34, p=0.023).

Table 2 reports the study outcomes. There was no significant change in HbA1c when comparing the pre-pandemic to the pandemic data (n=344, t=-1.78; 95% CI -0.21,0.01, p=0.076). However, more newly diagnosed T1DM patients presented in DKA (X^2 =12.94, p<0.001) and more patients required hospitalization at diagnosis in the unadjusted analysis (X^2 =50.94, p<0.001). In contrast, patients with established diabetes had less reported DKA (pre-pandemic 2018: 5.50%%, 2019: 5.80%; pandemic: 2.90%; p<0.001) and hospitalizations (pre-pandemic 2018: 9.00%, 2019: 9.80%; pandemic: 7.50%; p<0.001) during the pandemic. However, hospitalizations were not found to be significantly different during the pandemic in the GEE analysis (Table 3).

The burden of glucose fluctuations in patients with T1DM was sustained from pre-pandemic levels during the pandemic. A significant number of children reported hypoglycemia over the years and this trend continued into the pandemic (pre-pandemic 2018: 96.40%, 2019: 97.40%; pandemic: 96.80%; p=0.819). While hyperglycemic events were similarly reported in majority of patients in all years of study, there was an increase in reported hyperglycemia during the pandemic, compared to the pre-pandemic levels (pre-pandemic 2018: 83.70%, 2019: 82.00%; pandemic: 88.80%; p=0.011).

The results of the GEE analysis which model the association of the first year of the COVID-19 pandemic on glycemic control and diabetes-related morbidities, accounting for covariates that may influence these outcomes, are reported in Table 3. The analysis included 344 patients with available data. Due to missing data for BMI z-score during the pandemic, mostly due to missing hospital-measured heights to allow accurate calculation of BMI z-score, weight was instead adjusted for in the model and was not included as an outcome variable.

Table 3. Changes in Diabetes Control and Diabetes-Related Morbidities During the COVID-19 Pandemic (n=344)

	Effect Estimate		
	Mean difference (95% CI)	**Odds Ratio (95% CI)**	**p-value**
Main Outcome[+]			
HbA1c	-0.14 (-0.28,0.01)		0.058
Other Outcomes [++]			
DKA		0.30 (0.12,0.73)	0.009
Hospitalization		0.57 (0.31,1.04)	0.068
Hypoglycemia		1.11 (0.83,1.49)	0.484
Hyperglycemia		1.38 (1.12,1.71)	0.003

[+]Analysis was adjusted for age, sex, treatment type (injections vs. pump), sensor use, weight and diabetes-related morbidities (hypoglycemia, hyperglycemia, DKA and hospitalization)
[++]Analysis was adjusted for age, sex, treatment type (injections vs. pump) and sensor use
Abbreviations: 95% CI = 95% Confidence Interval, HbA1c = glycosylated hemoglobin A1c, DKA = diabetic ketoacidosis,

During the pandemic, participants with established diabetes had maintained their glycemic control (MD -0.14; 95% CI -0.28,0.01; p=0.058) with significantly less DKA (OR 0.30, 95% CI 0.12,0.73; p=0.009) with more hyperglycemia (OR 1.38, 95% CI 1.12,1.71; p=0.003) when compared to the pre-pandemic period.

There was no change in hospitalizations (OR 0.57, 95% CI 0.31,1.04; p=0.068) or hypoglycemic events (OR 1.11, 95% CI 0.83,1.49; p=0.484).

Table 4. Sensitivity Analysis using Multiple Imputations and Generalized Estimating Equation Model to Assess Glycemic Outcomes (n=346)

	Effect Estimate		
	Mean difference (95% CI)	**Odds Ratio (95% CI)**	**p-value**
Main Outcome[+]			
HbA1c	-0.09 (-0.30,0.12)		0.404
Other Outcomes[++]			
DKA		0.31 (0.12,0.79)	0.014
Hospitalization		0.58 (0.32,1.07)	0.081
Hypoglycemia		1.06 (0.80,1.40)	0.707
Hyperglycemia		1.26 (1.01,1.58)	0.042

[+]Analysis was adjusted for age, sex, treatment type (injections vs. pump), sensor use, weight and diabetes-related morbidities (hypoglycemia, hyperglycemia, DKA and hospitalization)
[++]Analysis was adjusted for age, sex, treatment type (injections vs. pump) and sensor use
Abbreviations: 95% CI = 95% Confidence Interval, HbA1c = glycosylated hemoglobin A1c, DKA = diabetic ketoacidosis

To address the concerns of missing data during the pandemic with virtual visits which restricted the amount of data collected and reported in clinic notes, we conducted multiple imputations and repeated the GEE model analyses which confirmed the same data trends (Table 4). The sensitivity analysis confirmed that the results are robust, and that missingness of data did not impact the results.

DISCUSSION

The COVID-19 pandemic fundamentally shifted models of care delivery for children and youth living with type 1 diabetes from in-person to virtual and hybrid models.[8,11-13] While evidence for the long-term impact of this shift in care delivery will take time to emerge, the short-term data are encouraging.

This retrospective study compared data for two years pre-pandemic to the first year of the pandemic for children and youth with T1DM attending a tertiary Canadian pediatric academic center. There were more newly diagnosed T1DM patients presenting in DKA during the pandemic when compared to the pre-pandemic phase. These trends were reversed in those with established diabetes. However, while the reported number of cases for these outcomes were relatively small, the data are consistent with current evidence reporting an increase in DKA and its severity at diagnosis.[18,44-48] These findings are largely attributed to delays in seeking care due to the fear of an increased risk in contracting the COVID-19 virus in a hospital setting, and that healthcare systems globally diverted finite resources to dealing with COVID-19, and patients were asked to defer access to care.[11,44] Further public education campaigns may be needed to raise awareness of diabetes presentation to prevent DKA and mitigate its severity at T1DM diagnosis.

Virtual and hybrid care models were associated with a stable HbA1c when compared to the exclusive in-person care models pre-pandemic. This conclusion, while contrary to our hypothesis, is consistent with some the emerging evidence for pandemic-related glycemic control trends.

While some studies reported similar stability in glycemic control[16,49-54], other studies even reported an improvement in glycemic control in children with T1DM.[19,55] The stability or potential improvement in glycemic control during the pandemic may be related to several factors, including enhanced attention to glycemic trends by children and their carers, increased patient-parent collaboration with managing glycemic trends, and the development of predictable diabetes management routines due to increased time spent at home and the cancellation of school and extra-curricular activities.[19,55] However, stable glycemic trends in T1DM were largely reported in studies from upper-middle or high income countries with infrastructure to conduct virtual visits and maintained access to treatment and monitoring modalities.[16,19,49,50,52,53,55] A study from India that was based on reported self-monitoring glucose data reported a worsening of glycemic control during the lockdowns.[56] This deterioration in glycemic control was attributed to the reduced availability of insulin and glucose test strip in the early stages of the pandemic.[56] For virtual and hybrid models of diabetes care to be effective and sustainable, the disparity in access to diabetes care teams and resources need to be eliminated. Adequate technological infrastructure that is available to families and healthcare systems need to be augmented globally. In addition, more widespread use of insulin pumps with glucose sensors and glucometers with capabilities to transmit data to healthcare teams caring for pediatric patients will likely enhance the impact of virtual care in T1DM.

Some studies reported an increase in DKA rates in children with established diabetes during the first lockdown within the first five months of the pandemic.[45,49] However, DKA rates stabilized and returned to baseline after the first COVID-19 wave, and in some case there was a reduction in DKA rates in youth during this period.[45,49] Our pandemic phase data are not consistent with these conclusions, with reduced DKA presentations, which may be related to the attention to glycemic trends and the awareness of the warning signs of DKA that may have led to early interventions to abort the DKA.[45,49,57-59]

Consistent with our results, there is evidence to suggest that the pandemic was not associated with increased hospitalization frequencies in those with established diabetes.[16] The rapid adoption of telemedicine, increased access to CGM and pump therapy, and increased attention to glycemic trends likely helped limit hospitalizations during the pandemic.[16]

The pandemic was also associated with higher rates of hyperglycemia when compared to the pre-pandemic phase despite stable glycemic control. It is possible that reported hyperglycemia is related to multiple factors, including more attention being paid to the glucose profile while in lockdown, the use of sensors that help detect glucose levels frequently, and changes in dietary patterns and physical activity levels, with children being less active and using technology for longer periods than in pre-pandemic times.[19,55,60-62] This possibility was also supported by the upward trend in BMI z-score. Further assessment of the factors contributing to this upward body mass trend is warranted.

The burden of hypoglycemia remained high throughout the pre-pandemic and pandemic phases, with most patients reporting at least one episode of hypoglycemia. These trends are consistent with the trends in the literature about hypoglycemia being a frequent accompaniment of T1DM.[63-66]

For people living with diabetes, glycemic variability and avoiding excursions of hypo- and hyperglycemia are a substantial burden to diabetes management.[67] Despite development of devices that increase monitoring and responsiveness to glycemic excursions, glycemic variability remain a relevant issue in the pediatric population.[63-66,68]

In studies that reported data from glucose sensors, including time in range (TIR) and time in hypoglycemia and hyperglycemia, most reported stability or improvement of TIR and glucose variability during the pandemic.[20,50,52-55] These trends during lockdown were transient, and predictably returned to baseline levels upon return to school and lifting of social distancing restrictions.[52,55]

Studies reported that physical activity decreased during lockdown, and most noted increases in weight measures.[49-52] This is consistent with the trends for weight percentile and BMI z-score seen in our participants.

The implementation of virtual care has been deemed acceptable to many families living with T1DM. Virtual consultations were satisfactory to patients and caregivers, with improved stress levels related to hospital visits and enhanced scheduling flexibility, with less need to disrupt school and work schedules and the preference of visits conducted in familiar settings.[17] [15]. However, it is important for families to have a choice in how to access care, as some families still prefer in-person consultations.[15] Evidence suggests that using sensors or insulin pumps and distance from clinics are not always accurate predictors of visit format preference.[18] Further studies are needed to personalize improved access to virtual diabetes care to maintain health outcomes.

Strengths & Limitations

This study compared glycemic control trends and diabetes-related outcomes before and after the start of the pandemic. The longitudinal data available for a relatively large sample allowed for the comparison of glycemic control over time to assess if there are emerging trends that need to be addressed. Using the GEE approach allowed the comparison and we appropriately handled missing data using multiple imputations.

There were some limitations to the present study. Our data is limited to only a single centre with diabetes patients, which may render the results less generalizable to other centres nationally and globally. We only reported the data from pediatric T1DM patients, which is less generalizable to other types of diabetes. With the disruption of clinical and laboratory services during the pandemic, most patients only had one or two HbA1c values, when compared to the pre-pandemic phase, where obtaining around four HbA1c values, annually, was the usual practice.

CONCLUSIONS

In patients with T1DM, glycemic control was comparable during the first year of the COVID-19 pandemic to the pre-pandemic phase. However, there was increased hyperglycemia.

This study highlights the potential applications of virtual and hybrid care models in pediatric diabetes care on an ongoing basis and beyond the pandemic. There is a need to understand the best design and delivery methods of these models so that they not only maintain glycemic control but strive to reduce diabetes-related co-morbidities and complications.

Author Contributions: R.R and M.C.S generated the research question. All authors conceptualized the study design. Data collection was done by R.R with the two acknowledged individuals, Ms. Saini and Ms. Cargnelli. Statistical analyses were performed by R.R, L.T, J.E.E, and M.C.S. All authors contributed to result interpretation. R.R and M.C.S drafted the manuscript and all authors edited and approved the final version. M.C.S is the guarantor.

Acknowledgements: We would like to thank Amandeep Saini and Claudia Cargnelli for their contributions in extracting data from patients charts for the study dataset.

Conflict of Interest: None reported.

References

1. Cucinotta D, Vanelli M. WHO declares COVID-19 a pandemic. *Acta Bio Medica: Atenei Parmensis*. 2020;91(1):157.
2. World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19-11 March 2020. Geneva, Switzerland; 2020.
3. COVID-19 Intervention Timeline in Canada. Canadian Institute for Health Information. https://www.cihi.ca/en/covid-19-intervention-timeline-in-canada
4. World Health Organization. *Infection prevention and control in the context of coronavirus disease (COVID-19): a living guideline, 25 April 2022: updated chapter: mask use, part 1: health care settings*. 2022.
5. Ryan RE, Parkhill A, Schonfeld L, et al. *What are relevant, feasible and effective approaches to promote acceptance, uptake and adherence to physical distancing measures for COVID-19 prevention and control?* World Health Organization. Regional Office for Europe; 2021.
6. Gayatri M, Irawaty DK. Family resilience during COVID-19 pandemic: A literature review. *The Family Journal*. 2021:10664807211023875.
7. Lemay DJ, Bazelais P, Doleck T. Transition to online learning during the COVID-19 pandemic. *Computers in Human Behavior Reports*. 2021;4:100130.
8. Imran N, Zeshan M, Pervaiz Z. Mental health considerations for children & adolescents in COVID-19 Pandemic. *Pakistan journal of medical sciences*. 2020;36(COVID19-S4):S67.
9. Patterson CC, Karuranga S, Salpea P, et al. Worldwide estimates of incidence, prevalence and mortality of type 1 diabetes in children and adolescents: Results from the International Diabetes Federation Diabetes Atlas. *Diabetes research and clinical practice*. 2019;157:107842.
10. Williams R, Karuranga S, Malanda B, et al. Global and regional estimates and projections of diabetes-related health expenditure: Results from the International Diabetes Federation Diabetes Atlas. *Diabetes Research and Clinical Practice*. 2020:108072.
11. Elbarbary NS, Dos Santos TJ, de Beaufort C, Agwu JC, Calliari LE, Scaramuzza AE. COVID-19 outbreak and pediatric diabetes: Perceptions of health care professionals worldwide. *Pediatric diabetes*. 2020;21(7):1083-1092.
12. World Health Organization. *Pulse survey on continuity of essential health services during the COVID-19 pandemic: interim report, 27 August 2020*. 2020.
13. Giuntella O, Hyde K, Saccardo S, Sadoff S. Lifestyle and mental health disruptions during COVID-19. *Proceedings of the National Academy of Sciences*. 2021;118(9)
14. World Health Organization. *Second round of the national pulse survey on continuity of essential health services during the COVID-19 pandemic: interim report, 22 April 2021*. 2021.
15. Fung A, Irvine M, Ayub A, Ziabakhsh S, Amed S, Hursh BE. Evaluation of telephone and virtual visits for routine pediatric diabetes care during the COVID-19 pandemic. *Journal of clinical & translational endocrinology*. 2020;22:100238.
16. Choudhary A, Adhikari S, White PC. Impact of the COVID-19 pandemic on management of children and adolescents with Type 1 diabetes. *BMC pediatrics*. 2022;22(1):1-7.
17. Braune K, Boss K, Schmidt-Herzel J, et al. Shaping workflows in digital and remote diabetes care during the covid-19 pandemic via service design: prospective, longitudinal, open-label feasibility trial. *JMIR mHealth and uHealth*. 2021;9(4):e24374.
18. Kaushal T, Ambler-Osborn L, Turcotte C, Quinn H, Laffel L. Rapid adoption of telemedicine along with emergent use of continuous glucose monitors in the ambulatory care of

young persons with new-onset type 1 diabetes in the time of COVID-19: a case series. *Telemedicine and e-Health*. 2022;28(1):107-114.
19. Lazzeroni P, Motta M, Monaco S, et al. Improvement in glycaemic control in paediatric and young adult type 1 diabetes patients during COVID-19 pandemic: role of telemedicine and lifestyle changes. *Acta Bio Medica: Atenei Parmensis*. 2021;92(5)
20. Rachmiel M, Lebenthal Y, Mazor-Aronovitch K, et al. Glycaemic control in the paediatric and young adult population with type 1 diabetes following a single telehealth visit-what have we learned from the COVID-19 lockdown? *Acta Diabetologica*. 2021;58(6):697-705.
21. Wood CL, Clements SA, McFann K, Slover R, Thomas JF, Wadwa RP. Use of telemedicine to improve adherence to American Diabetes Association standards in pediatric type 1 diabetes. *Diabetes technology & therapeutics*. 2016;18(1):7-14.
22. Levin K, Madsen JR, Petersen I, Wanscher CE, Hangaard J. Telemedicine diabetes consultations are cost-effective, and effects on essential diabetes treatment parameters are similar to conventional treatment: 7-year results from the Svendborg Telemedicine Diabetes Project. SAGE Publications; 2013.
23. American Diabetes Association. 13. Children and adolescents: standards of medical care in diabetes− 2020. Diabetes Care. 2020 Jan 1;43(Supplement 1):S163-82.
24. Diabetes Canada Clinical Practice Guidelines Expert Committee. Diabetes Canada 2018 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada. Can J Diabetes. 2018;42(Suppl 1):S1-S325.
25. Hattersley AT, Greeley SA, Polak M, et al. ISPAD Clinical Practice Consensus Guidelines 2018: Stages of type 1 diabetes in children and adolescents. 2018;
26. Wittmeier KD, Protudjer JL, Wicklow BA. Reflections on virtual Care for Chronic Conditions During the COVID-19 pandemic. *Canadian Journal of Diabetes*. 2021;45(1):1-2.
27. Canadian Medical Association. Virtual care in Canada: Discussion paper. https://www.cma.ca/sites/default/files/pdf/News/Virtual_Care_discussionpaper_v2EN.pdf.
28. De Guzman KR, Snoswell CL, Taylor ML, et al. A systematic review of pediatric telediabetes service models. *Diabetes Technology & Therapeutics*. 2020;22(8):623-638.
29. Zhao X, Huang H, Zheng S. Effectiveness of Internet and Phone-Based Interventions on Diabetes Management of Children and Adolescents With Type 1 Diabetes: A Systematic Review. *Worldviews on Evidence-Based Nursing*. 2021;18(3):217-225.
30. Raymond JK, Berget CL, Driscoll KA, Ketchum K, Cain C, “Fred” Thomas JF. CoYoT1 clinic: innovative telemedicine care model for young adults with type 1 diabetes. *Diabetes Technology & Therapeutics*. 2016;18(6):385-390.
31. Raymond JK, Reid MW, Fox S, et al. Adapting home telehealth group appointment model (CoYoT1 clinic) for a low SES, publicly insured, minority young adult population with type 1 diabetes. Article. *Contemporary Clinical Trials*. Jan 2020;88:9. 105896. doi:10.1016/j.cct.2019.105896
32. Cobry EC, Reznick-Lipina T, Pyle L, et al. Diabetes Technology Use in Remote Pediatric Patients with Type 1 Diabetes Using Clinic-to-Clinic Telemedicine. *Diabetes technology & therapeutics*. 2022;24(1):67-74.
33. Tejera-Perez C, Moreno-Pérez Ó, Rios J, Reyes-García R. People living with type 1 diabetes point of view in COVID-19 times (COVIDT1 study): Disease impact, health system pitfalls and lessons for the future. *Diabetes research and clinical practice*. 2021;171:108547.
34. American Diabetes Association. 2. Classification and diagnosis of diabetes: Standards of Medical Care in Diabetes—2020. Diabetes care. 2020 Jan 1;43(Supplement 1):S14-31.

35. Must A, Anderson S. Body mass index in children and adolescents: considerations for population-based applications. *International journal of obesity*. 2006;30(4):590-594.
36. Wolfsdorf JI, Glaser N, Agus M, et al. ISPAD Clinical Practice Consensus Guidelines 2018: Diabetic ketoacidosis and the hyperglycemic hyperosmolar state. *Pediatric diabetes*. 2018;19:155-177.
37. O'brien RM. A caution regarding rules of thumb for variance inflation factors. *Quality & quantity*. 2007;41(5):673-690.
38. Zeger SL, Liang K-Y. Longitudinal data analysis for discrete and continuous outcomes. *Biometrics*. 1986:121-130.
39. Diabetes Canada Clinical Practice Guidelines Expert Committee. Diabetes Canada 2018 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada . Can J Diabetes. 2018;42(Suppl 1):S1-S325.
40. Ballinger GA. Using generalized estimating equations for longitudinal data analysis. *Organizational research methods*. 2004;7(2):127-150.
41. Schneeweiss S. Sensitivity analysis and external adjustment for unmeasured confounders in epidemiologic database studies of therapeutics. *Pharmacoepidemiology and drug safety*. 2006;15(5):291-303.
42. Thabane L, Mbuagbaw L, Zhang S, et al. A tutorial on sensitivity analyses in clinical trials: the what, why, when and how. *BMC medical research methodology*. 2013;13(1):1-12.
43. IBM Corp. Released 2021. IBM SPSS Statistics for Macintosh, Version 28.0. Armonk, NY: IBM Corp.
44. Kamrath C, Mönkemöller K, Biester T, et al. Ketoacidosis in children and adolescents with newly diagnosed type 1 diabetes during the COVID-19 pandemic in Germany. *Jama*. 2020;324(8):801-804.
45. Danne T, Lanzinger S, de Bock M, et al. A worldwide perspective on COVID-19 and diabetes management in 22,820 children from the SWEET project: diabetic ketoacidosis rates increase and glycemic control is maintained. *Diabetes technology & therapeutics*. 2021;23(9):632-641.
46. Wolf RM, Noor N, Izquierdo R, et al. Increase in newly diagnosed type 1 diabetes in youth during the COVID-19 pandemic in the United States: A multi-center analysis. *Pediatric Diabetes*. 2022;
47. Unsworth R, Wallace S, Oliver NS, et al. New-onset type 1 diabetes in children during COVID-19: multicenter regional findings in the UK. *Diabetes Care*. 2020;43(11):e170-e171.
48. Marks BE, Khilnani A, Meyers A, et al. Increase in the Diagnosis and Severity of Presentation of Pediatric Type 1 and Type 2 Diabetes During the COVID-19 Pandemic. *Hormone research in paediatrics*. 2021;94(7-8):275-284.
49. Hammersen J, Reschke F, Tittel SR, et al. Metabolic control during the SARS-CoV-2 lockdown in a large German cohort of pediatric patients with type 1 diabetes: results from the DPV initiative. *Pediatric Diabetes*. 2022;23(3):351-361.
50. Minuto N, Bassi M, Montobbio C, et al. The effect of lockdown and physical activity on glycemic control in Italian children and young patients with type 1 diabetes. *Frontiers in endocrinology*. 2021;12
51. Shah N, Karguppikar M, Bhor S, Ladkat D, Khadilkar V, Khadilkar A. Impact of lockdown for COVID-19 pandemic in Indian children and youth with type 1 diabetes from different socio-economic classes. *Journal of Pediatric Endocrinology and Metabolism*. 2021;34(2):217-223.

52. Wu X, Luo S, Zheng X, et al. Glycemic control in children and teenagers with type 1 diabetes around lockdown for COVID-19: A continuous glucose monitoring-based observational study. *Journal of diabetes investigation*. 2021;12(9):1708-1717.
53. Tinti D, Savastio S, Grosso C, et al. Impact of lockdown during COVID-19 emergency on glucose metrics of children and adolescents with type 1 diabetes in Piedmont, Italy. *Acta Diabetologica*. 2021;58(7):959-961.
54. Silverii GA, Delli Poggi C, Dicembrini I, Monami M, Mannucci E. Glucose control in diabetes during home confinement for the first pandemic wave of COVID-19: a meta-analysis of observational studies. *Acta diabetologica*. 2021;58(12):1603-1611.
55. Lombardo F, Salzano G, Bombaci B, et al. Has COVID-19 lockdown improved glycaemic control in pediatric patients with type 1 diabetes? An analysis of continuous glucose monitoring metrics. *diabetes research and clinical practice*. 2021;178:108988.
56. Verma A, Rajput R, Verma S, Balania VK, Jangra B. Impact of lockdown in COVID 19 on glycemic control in patients with type 1 Diabetes Mellitus. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews*. 2020;14(5):1213-1216.
57. Chanchlani N, Buchanan F, Gill PJ. Addressing the indirect effects of COVID-19 on the health of children and young people. *CMAJ*. 2020;192(32):E921-E927.
58. Davis AL, Sunderji A, Marneni SR, et al. Caregiver-reported delay in presentation to pediatric emergency departments for fear of contracting COVID-19: a multi-national cross-sectional study. *Canadian Journal of Emergency Medicine*. 2021;23(6):778-786.
59. Survey on Access to Health Care and Pharmaceuticals During the Pandemic, March 2020 to May 2021. Statistics Canada. https://www150.statcan.gc.ca/n1/daily-quotidien/211123/dq211123b-eng.htm
60. Stockwell S, Trott M, Tully M, et al. Changes in physical activity and sedentary behaviours from before to during the COVID-19 pandemic lockdown: a systematic review. *BMJ open sport & exercise medicine*. 2021;7(1):e000960.
61. Wicaksana AL, Hertanti NS, Ferdiana A, Pramono RB. Diabetes management and specific considerations for patients with diabetes during coronavirus diseases pandemic: A scoping review. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews*. 2020;14(5):1109-1120.
62. Okuyama J, Seto S, Fukuda Y, et al. Mental health and physical activity among children and adolescents during the COVID-19 pandemic. *The Tohoku journal of experimental medicine*. 2021;253(3):203-215.
63. Wintergerst KA, Buckingham B, Gandrud L, Wong BJ, Kache S, Wilson DM. Association of hypoglycemia, hyperglycemia, and glucose variability with morbidity and death in the pediatric intensive care unit. *Pediatrics*. 2006;118(1):173-179.
64. Urakami T. Severe hypoglycemia: is it still a threat for children and adolescents with type 1 diabetes? *Frontiers in Endocrinology*. 2020:609.
65. Bulsara MK, Holman CDAJ, Davis EA, Jones TW. The impact of a decade of changing treatment on rates of severe hypoglycemia in a population-based cohort of children with type 1 diabetes. *Diabetes care*. 2004;27(10):2293-2298.
66. Karges B, Rosenbauer J, Kapellen T, et al. Hemoglobin A1c levels and risk of severe hypoglycemia in children and young adults with type 1 diabetes from Germany and Austria: a trend analysis in a cohort of 37,539 patients between 1995 and 2012. *PLoS medicine*. 2014;11(10):e1001742.

67. Brazeau A-S, Messier V, Talbo M, et al. Type 1 Diabetes Population Surveillance Through the BETTER Patient-Engagement Registry: Development and Baseline Characteristics. *Canadian Journal of Diabetes*. 2022;
68. Rewers A, Chase HP, Mackenzie T, et al. Predictors of acute complications in children with type 1 diabetes. *Jama*. 2002;287(19):2511-2518.

Chapter 3

3.1 Association of the COVID-19 Pandemic on Measures of Glycemic Control

In this present study, we report that glycemic control, as measured by HbA1c, was not found to deteriorate during the pandemic. The pandemic was also not significantly associated with increased hospitalization or reported hypoglycemic events. However, there was significant association of the pandemic on the reported increase in hyperglycemia and reduction in DKA events in the included participants. These results were consistent in our sensitivity analysis.

These results oppose the original hypothesis that markers of glycemic control and diabetes-related adverse events would deteriorate during the pandemic. It was anticipated that the burden caused by the COVID-19 pandemic coupled with the novelty of virtual consultations in diabetes care would cause diabetes management would be suboptimal. Instead, and considering the novelty of virtual care on such wide scale, some outcomes of interest were found to be stable or to be less frequent during the pandemic, apart from hyperglycemia. These results are largely in agreement with the existing body of evidence in the field. In a recent meta-analysis and in some published studies, there was no significant changes reported in HbA1c with lockdown, compared to pre-lockdown data in children and adults with T1DM[43,46,51,52], while others reported improvements in glycemic control that were transient for most patients, as in the months following the lockdown glycemic control returned to baseline values.[50,53]

Many studies note a reduction in physical activity during the pandemic, as a result of stay-at-home orders and cancelled organized activity.[44,46,54] While this was found to be challenging, and in some cases detrimental to weight and BMI[50], the negative impacts may have been counteracted with reported increase in sleep duration and spending more time on diabetes management with parental supervision.[45,46,50,54] It is also suggested that with cancelled school and organized activity, diabetes management became more predictable and unexpected excursions in blood glucose levels could be managed more immediately and effectively.[44,46,50] Many patients still had access to support from their diabetes care team during the pandemic, which likely also aided in maintaining glycemic control during a time of perceived stress.[44-46]

Some studies suggest that patients presenting with new onset diabetes were worse off when compared to previous years.[33,55-57] There were reports of increased numbers of newly diagnosed pediatric T1DM patients, with a greater proportion presenting in DKA at diagnosis compared to one year pre-pandemic.[57] This is consistent with research from Germany, Italy and the United Kingdom.[56,58-60] These findings may be attributed to avoidance or delays in seeking medical care during the pandemic, which may have led to a more severe illness at presentation.[57-60] In our clinic, we did see the number of patients diagnosed with T1DM rise in 2020 when compared to cases diagnosed in 2018-2019. Consistently high presentation of new diabetes in hospital is expected and consistent with our current care models, where most patients are treated in urgent care settings initially, and provided education in hospital.[4]

3.2 Virtual Diabetes Care

Virtual care during the pandemic has been widely accredited for maintained or improved glycemic control found in pediatric T1DM populations.[44-47,52] The caregivers of children with T1DM found virtual consultations to be beneficial to themselves and their child.[47] These caregivers noted benefits including reduced stress accompanied with hospital visits, increased flexibility of meeting at different times of the day and increased comfort in having visits in familiar settings.[47] Caregivers found reviewing glycemic control data together with healthcare providers to be beneficial and were overall satisfied with the virtual diabetes support they received during the pandemic.[47]

These findings were echoed in a study conducted by Fung et al., where families of children with diabetes stated that they found virtual diabetes visits to be usable and feasible.[49] Most families from this study stated that they would opt in to receive virtual visits again in the future. However, there were still close to 25% of families would want all future visits to be in-person.[49] In assessing characteristics that may determine which families would prefer virtual visits, Fung et al. reported that technological experience (i.e., utilizing CGM or insulin pumps) or distance from clinics were not true predictors. Increased refinement is necessary in understanding which families would benefit most, or potentially harmed most, with a transition to virtual care.

In patients newly diagnosed with diabetes during the pandemic, provision of technological diabetes management devices was found to be valuable. Kaushal et al. suggested that early initiation of CGM was associated with improved glycemic control and fostered early acceptance of device wear.[55] Patients and their families found the data sharing capabilities to be convenient and attributed this feature to better glucose monitoring behaviour.[55] These patients and their families also found virtual consultations to be of increased convenience as they did not have to leave work to attend clinic visits and multiple households could join virtual consultations easily.[55]

Barriers to virtual consultations were also highlighted during the pandemic. Patients attending virtual consultations could not be assessed for anthropometric values.[61] This is particularly concerning for children with diabetes, as excursions of normal weight, height and/or BMI may suggest suboptimal glycemic control that can worsen if not adequately addressed.[4,5,9] Fluctuations in body mass may result from changes in physical activity levels and carbohydrate intake, which would necessitate adjustments to insulin regimen in order to uphold optimal glycemic control.[43-46] Virtual consultations also increased responsibility on patients and their families to obtain bloodwork from within the community in their own time, rather than with a clinic visit.[61] As a result, many patients were missing crucial lab data on HbA1c and markers of diabetes-related morbidities.[61]

Virtual consultations can take a toll on users, as some patients with T1DM and their caregivers reported a lack of emotional support and increased neglect from healthcare professionals through virtual consultations.[62,63] With many forms of virtual communication, non-verbal cues normally used to show care, empathy and listening are lost, which may cause feelings of disconnect and neglect from patients. It is crucial that with virtual care, healthcare providers adjust their communication methods to account for disruptions to normal communication, to ensure patients still feel safe and cared for.[62,63]

Patients and families who faced technical problems during virtual clinic visits, or who did not have the appropriate devices, internet connection or skills to participate were found to opt out of virtual visits in the study by Rachmiel et al.[63] This finding highlights the need for appropriate provision of resources and education for patients who are required to attend virtual visits. For patients who lack access to joining virtual visits should instead be provided with accommodations to attend in person.

3.3 Future Considerations

While virtual care provides many benefits to pediatric patients with T1DM and their families, there are still some barriers that need to be addressed. A tailored approach to healthcare delivery should be adopted, whereby patient needs are at the center of care delivery. Patients and their families should have a choice as to whether they would prefer in-person versus virtual clinic visits. That is, in cases where patients are more comfortable with in-person visits, or are due for certain tests to be completed, in-person services may be more suitable. On the other hand, patients and families who are enthusiastic about virtual visits should be equally provided with this option.

Prior to adopting virtual consultations for all pediatric diabetes patients, it is imperative that future research evaluates the effectiveness of virtual consultations after the pandemic. Restrictions and lockdown measures in place during the pandemic were unique circumstances that likely played a large role in the maintenance or improvement of glycemic control reported in many studies. However, as these restrictions continue to lift and normalcy is reintroduced, it is important to also re-assess virtual consultations and whether maintenance or improvement in glycemic control is still seen. Additionally, the studies reporting on glycemic control with virtual consultations during the pandemic were largely observational studies in single centres. These studies are subjected to bias as well as issues with validity and reliability and cannot yet be generalized to other locations or into guidelines. Thus, high quality, longitudinal studies are needed to assess the effects of virtual visits compared to in-person clinic visits in children with T1DM.

Chapter 4

The COVID-19 pandemic necessitated a rapid adoption of virtual care in the field of pediatric diabetes during the time of lockdown and restrictions of face-to-face interactions. From this study, the pandemic did not lead to an increase in HbA1c in children with T1DM. In patients with established diabetes, the pandemic was significantly associated with an increase in reported hyperglycemia and a decrease in DKA. There was also no association of the pandemic with reported hospitalization and hypoglycemic events, and these outcomes remained stable during the pandemic. These results were confirmed with the sensitivity analysis.

There was a significant increase in patients newly diagnosed with T1DM during the pandemic, and in their presentation with DKA and hospitalization. These results provide important insights into how patients and healthcare systems responded to the pandemic and the virtual services offered during this time.

Futher research is needed before widescale recommendation of virtual consultations to replace in-person clinic visits. As well, barriers to accessing virtual care needs to be addressed before widespread recommendation and implementation. While virtual care has numerous benefits and is largely accepted by patients and families, these stakeholders should ultimately be provided with the consultations delivered according to their needs.

References

1. Patterson CC, Karuranga S, Salpea P, et al. Worldwide estimates of incidence, prevalence and mortality of type 1 diabetes in children and adolescents: Results from the International Diabetes Federation Diabetes Atlas. *Diabetes research and clinical practice*. 2019;157:107842.
2. Williams R, Karuranga S, Malanda B, et al. Global and regional estimates and projections of diabetes-related health expenditure: Results from the International Diabetes Federation Diabetes Atlas. *Diabetes Research and Clinical Practice*. 2020:108072.
3. American Diabetes Association. 2. Classification and diagnosis of diabetes: Standards of Medical Care in Diabetes—2020. Diabetes care. 2020 Jan 1;43(Supplement 1):S14-31.
4. Diabetes Canada Clinical Practice Guidelines Expert Committee. Diabetes Canada 2018 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada. Can J Diabetes. 2018;42(Suppl 1):S1-S325.
5. Hattersley AT, Greeley SA, Polak M, et al. ISPAD Clinical Practice Consensus Guidelines 2018: Stages of type 1 diabetes in children and adolescents. 2018;
6. Redondo MJ, Steck AK, Pugliese A. Genetics of type 1 diabetes. *Pediatric diabetes*. 2018;19(3):346-353.
7. Rewers M, Ludvigsson J. Environmental risk factors for type 1 diabetes. *The Lancet*. 2016;387(10035):2340-2348.
8. D'Angeli MA, Merzon E, Valbuena LF, Tirschwell D, Paris CA, Mueller BA. Environmental factors associated with childhood-onset type 1 diabetes mellitus: an exploration of the hygiene and overload hypotheses. *Archives of pediatrics & adolescent medicine*. 2010;164(8):732-738.
9. American Diabetes Association. 13. Children and adolescents: standards of medical care in diabetes− 2020. Diabetes Care. 2020 Jan 1;43(Supplement 1):S163-82.
10. Bernstein CM, Stockwell MS, Gallagher MP, Rosenthal SL, Soren K. Mental health issues in adolescents and young adults with type 1 diabetes: prevalence and impact on glycemic control. *Clinical pediatrics*. 2013;52(1):10-15.
11. Pinhas-Hamiel O, Hamiel U, Levy-Shraga Y. Eating disorders in adolescents with type 1 diabetes: challenges in diagnosis and treatment. *World journal of diabetes*. 2015;6(3):517.
12. Crowley R, Wolfe I, Lock K, McKee M. Improving the transition between paediatric and adult healthcare: a systematic review. *Archives of disease in childhood*. 2011;96(6):548-553.
13. Seguin D, Kuenzel E, Morton JB, Duerden EG. School's out: parenting stress and screen time use in school-age children during the COVID-19 pandemic. *Journal of Affective Disorders Reports*. 2021;6:100217.
14. Canadian Internet Use Survey. https://www150.statcan.gc.ca/n1/daily-quotidien/210622/dq210622b-eng.htm
15. De Guzman KR, Snoswell CL, Taylor ML, et al. A systematic review of pediatric telediabetes service models. *Diabetes Technology & Therapeutics*. 2020;22(8):623-638.
16. Zhao X, Huang H, Zheng S. Effectiveness of Internet and Phone-Based Interventions on Diabetes Management of Children and Adolescents With Type 1 Diabetes: A Systematic Review. *Worldviews on Evidence-Based Nursing*. 2021;18(3):217-225.
17. Shah AC, Badawy SM. Telemedicine in pediatrics: systematic review of randomized controlled trials. *JMIR pediatrics and parenting*. 2021;4(1):e22696.
18. Dimitri P. Child health technology: shaping the future of paediatrics and child health and improving NHS productivity. *Archives of Disease in Childhood*. 2019;104(2):184-188.

19. Cobry EC, Reznick-Lipina T, Pyle L, et al. Diabetes Technology Use in Remote Pediatric Patients with Type 1 Diabetes Using Clinic-to-Clinic Telemedicine. *Diabetes technology & therapeutics*. 2022;24(1):67-74.
20. Wood CL, Clements SA, McFann K, Slover R, Thomas JF, Wadwa RP. Use of telemedicine to improve adherence to American Diabetes Association standards in pediatric type 1 diabetes. *Diabetes technology & therapeutics*. 2016;18(1):7-14.
21. Levin K, Madsen JR, Petersen I, Wanscher CE, Hangaard J. Telemedicine diabetes consultations are cost-effective, and effects on essential diabetes treatment parameters are similar to conventional treatment: 7-year results from the Svendborg Telemedicine Diabetes Project. SAGE Publications; 2013.
22. Sherr JL, Tauschmann M, Battelino T, et al. ISPAD Clinical Practice Consensus Guidelines 2018: Diabetes technologies. Article; Proceedings Paper. *Pediatric Diabetes*. Oct 2018;19:302-325. doi:10.1111/pedi.12731
23. Garg SK, Weinzimer SA, Tamborlane WV, et al. Glucose outcomes with the in-home use of a hybrid closed-loop insulin delivery system in adolescents and adults with type 1 diabetes. *Diabetes technology & therapeutics*. 2017;19(3):155-163.
24. Lang EG, King BR, Miller MN, Dunn SV, Price DA, Foskett DC. Initiation of insulin pump therapy in children at diagnosis of type 1 diabetes resulted in improved long-term glycemic control. *Pediatric Diabetes*. 2017;18(1):26-32.
25. Klonoff DC, Ahn D, Drincic A. Continuous glucose monitoring: a review of the technology and clinical use. *Diabetes Research and Clinical Practice*. 2017;133:178-192.
26. Breton MD, Kanapka LG, Beck RW, et al. A randomized trial of closed-loop control in children with type 1 diabetes. *New England Journal of Medicine*. 2020;383(9):836-845.
27. Xu Y, Xu L, Zhao W, et al. Effectiveness of a WeChat combined continuous flash glucose monitoring system on glycemic control in juvenile type 1 diabetes mellitus management: randomized controlled trial. *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy*. 2021;14:1085.
28. Brown SJ, Lieberman DA, Gemeny BA, Fan YC, Wilson DM, Pasta DJ. Educational video game for juvenile diabetes: Results of a controlled trial. Article. *Medical Informatics*. Jan-Mar 1997;22(1):77-89. doi:10.3109/14639239709089835
29. Cucinotta D, Vanelli M. WHO declares COVID-19 a pandemic. *Acta Bio Medica: Atenei Parmensis*. 2020;91(1):157.
30. COVID-19 Intervention Timeline in Canada. Canadian Institute for Health Information. https://www.cihi.ca/en/covid-19-intervention-timeline-in-canada
31. Shekerdemian LS, Mahmood NR, Wolfe KK, et al. Characteristics and outcomes of children with coronavirus disease 2019 (COVID-19) infection admitted to US and Canadian pediatric intensive care units. *JAMA pediatrics*. 2020;
32. Rabbone I, Schiaffini R, Cherubini V, Maffeis C, Scaramuzza A. Has COVID-19 delayed the diagnosis and worsened the presentation of type 1 diabetes in children? *Diabetes Care*. 2020;43(11):2870-2872.
33. Kamrath C, Mönkemöller K, Biester T, et al. Ketoacidosis in children and adolescents with newly diagnosed type 1 diabetes during the COVID-19 pandemic in Germany. *Jama*. 2020;324(8):801-804.
34. Ebekozien OA, Noor N, Gallagher MP, Alonso GT. Type 1 Diabetes and COVID-19: Preliminary Findings From a Multicenter Surveillance Study in the US. *Diabetes Care*. 2020;

35. Verma A, Rajput R, Verma S, Balania VK, Jangra B. Impact of lockdown in COVID 19 on glycemic control in patients with type 1 Diabetes Mellitus. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews*. 2020;14(5):1213-1216.
36. Wittmeier KD, Protudjer JL, Wicklow BA. Reflections on virtual Care for Chronic Conditions During the COVID-19 pandemic. *Canadian Journal of Diabetes*. 2021;45(1):1-2.
37. Canadian Medical Association. Virtual care in Canada: Discussion paper. https://www.cma.ca/sites/default/files/pdf/News/Virtual_Care_discussionpaper_v2EN.pdf.
38. Detsky AS, Bogoch II. COVID-19 in Canada: experience and response. *Jama*. 2020;324(8):743-744.
39. Detsky AS, Bogoch II. COVID-19 in Canada: Experience and Response to Waves 2 and 3. *JAMA*. 2021;326(12):1145-1146.
40. Kelley L, Phung M, Stamenova V, et al. Exploring how virtual primary care visits affect patient burden of treatment. *International Journal of Medical Informatics*. 2020;141:104228.
41. Falk W. The state of virtual care in Canada as of wave three of the COVID-19 pandemic: An early diagnostic and policy recommendations. 2021;
42. Kronfli C. *Realizing the Full Potential of Virtual Care in Ontario*. Ontario Chamber of Commerce; 2020.
43. Hammersen J, Reschke F, Tittel SR, et al. Metabolic control during the SARS-CoV-2 lockdown in a large German cohort of pediatric patients with type 1 diabetes: results from the DPV initiative. *Pediatric Diabetes*. 2022;23(3):351-361.
44. Minuto N, Bassi M, Montobbio C, et al. The effect of lockdown and physical activity on glycemic control in Italian children and young patients with type 1 diabetes. *Frontiers in endocrinology*. 2021;12
45. Shah N, Karguppikar M, Bhor S, Ladkat D, Khadilkar V, Khadilkar A. Impact of lockdown for COVID-19 pandemic in Indian children and youth with type 1 diabetes from different socio-economic classes. *Journal of Pediatric Endocrinology and Metabolism*. 2021;34(2):217-223.
46. Wu X, Luo S, Zheng X, et al. Glycemic control in children and teenagers with type 1 diabetes around lockdown for COVID-19: A continuous glucose monitoring-based observational study. *Journal of diabetes investigation*. 2021;12(9):1708-1717.
47. Braune K, Boss K, Schmidt-Herzel J, et al. Shaping workflows in digital and remote diabetes care during the covid-19 pandemic via service design: prospective, longitudinal, open-label feasibility trial. *JMIR mHealth and uHealth*. 2021;9(4):e24374.
48. Glauser W. Virtual care is here to stay, but major challenges remain. *Canadian Medical Association Journal*. 2020;192(30):E868-E869.
49. Fung A, Irvine M, Ayub A, Ziabakhsh S, Amed S, Hursh BE. Evaluation of telephone and virtual visits for routine pediatric diabetes care during the COVID-19 pandemic. *Journal of clinical & translational endocrinology*. 2020;22:100238.
50. Lazzeroni P, Motta M, Monaco S, et al. Improvement in glycaemic control in paediatric and young adult type 1 diabetes patients during COVID-19 pandemic: role of telemedicine and lifestyle changes. *Acta Bio Medica: Atenei Parmensis*. 2021;92(5)
51. Silverii GA, Delli Poggi C, Dicembrini I, Monami M, Mannucci E. Glucose control in diabetes during home confinement for the first pandemic wave of COVID-19: a meta-analysis of observational studies. *Acta diabetologica*. 2021;58(12):1603-1611.
52. Choudhary A, Adhikari S, White PC. Impact of the COVID-19 pandemic on management of children and adolescents with Type 1 diabetes. *BMC pediatrics*. 2022;22(1):1-7.

53. Lombardo F, Salzano G, Bombaci B, et al. Has COVID-19 lockdown improved glycaemic control in pediatric patients with type 1 diabetes? An analysis of continuous glucose monitoring metrics. *diabetes research and clinical practice*. 2021;178:108988.
54. Tinti D, Savastio S, Grosso C, et al. Impact of lockdown during COVID-19 emergency on glucose metrics of children and adolescents with type 1 diabetes in Piedmont, Italy. *Acta Diabetologica*. 2021;58(7):959-961.
55. Kaushal T, Ambler-Osborn L, Turcotte C, Quinn H, Laffel L. Rapid adoption of telemedicine along with emergent use of continuous glucose monitors in the ambulatory care of young persons with new-onset type 1 diabetes in the time of COVID-19: a case series. *Telemedicine and e-Health*. 2022;28(1):107-114.
56. Danne T, Lanzinger S, de Bock M, et al. A worldwide perspective on COVID-19 and diabetes management in 22,820 children from the SWEET project: diabetic ketoacidosis rates increase and glycemic control is maintained. *Diabetes technology & therapeutics*. 2021;23(9):632-641.
57. Wolf RM, Noor N, Izquierdo R, et al. Increase in newly diagnosed type 1 diabetes in youth during the COVID-19 pandemic in the United States: A multi-center analysis. *Pediatric Diabetes*. 2022;
58. Kamrath C, Rosenbauer J, Eckert AJ, et al. Glycated hemoglobin at diagnosis of type 1 diabetes and at follow-up in children and adolescents during the COVID-19 pandemic in Germany. *Pediatric Diabetes*. 2022;
59. Unsworth R, Wallace S, Oliver NS, et al. New-onset type 1 diabetes in children during COVID-19: multicenter regional findings in the UK. *Diabetes Care*. 2020;43(11):e170-e171.
60. Marks BE, Khilnani A, Meyers A, et al. Increase in the Diagnosis and Severity of Presentation of Pediatric Type 1 and Type 2 Diabetes During the COVID-19 Pandemic. *Hormone research in paediatrics*. 2021;94(7-8):275-284.
61. Silva C, Zhang Q, Bone JN, Amed S. Anthropometric measurements and laboratory investigations in children and youth with type 1 diabetes before and during the COVID-19 pandemic. *Canadian Journal of Diabetes*. 2022;
62. Tejera-Perez C, Moreno-Pérez Ó, Rios J, Reyes-García R. People living with type 1 diabetes point of view in COVID-19 times (COVIDT1 study): Disease impact, health system pitfalls and lessons for the future. *Diabetes research and clinical practice*. 2021;171:108547.
63. Rachmiel M, Lebenthal Y, Mazor-Aronovitch K, et al. Glycaemic control in the paediatric and young adult population with type 1 diabetes following a single telehealth visit-what have we learned from the COVID-19 lockdown? *Acta Diabetologica*. 2021;58(6):697-705.