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TYPE 1 DIABETES MELLITUS: BEFORE, DURING, AND AFTER COVID-19

ARTIGO DE REVISÃO NARRATIVA

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TYPE 1 DIABETES MELLITUS: BEFORE, DURING, AND AFTER COVID-19

Artigo de Revisão Narrativa

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RESUMO

O surto global do novo coronavírus SRAS-CoV-2 tem sido incomparável e nunca antes visto. Mesmo antes da realização de um estudo detalhado da doença coronavírus 2019 (COVID-19), foram expressas preocupações substanciais sobre o potencial impacto do vírus em pessoas com doenças crónicas, tais como a diabetes tipo 1.

A diabetes mellitus tipo 1 (T1DM) é uma doença autoimune definida pela morte de células beta pancreáticas produtoras de insulina, resultando num défice de insulina. É uma das doenças crónicas mais comuns entre crianças e adolescentes, causando graves consequências a curto prazo, bem como uma série de complicações macrovasculares ou microvasculares a longo prazo. Em crianças com diabetes, a cetoacidose diabética continua a ser a principal causa de morbilidade e mortalidade.

Esta revisão fornece uma visão geral dos aspetos atuais da diabetes tipo 1, incluindo a sua epidemiologia, diagnóstico, bem como um melhor conhecimento sobre a sua gestão e uma breve revisão das suas principais complicações. Fornece-se informação adicional relativa ao vírus SRAS-CoV-2 e uma abordagem ao quadro clínico dos doentes com COVID-19, de maneira a compreender melhor a pandemia e perceber o seu impacto sobre a população em geral. Por fim, com o objetivo final de relatar e conhecer as principais preocupações e desafios da população pediátrica com diabetes tipo 1 durante a pandemia de COVID-19, foram discutidos tópicos tais como novos diagnósticos de diabetes tipo 1 durante a pandemia, o impacto na monitorização da glucose e telemedicina, os doentes diabéticos tipo 1 com COVID-19 e a sua gravidade e uma breve revisão sobre as diferenças entre os confinamentos, com a finalidade de estabelecer algumas ideias-chave sobre uma melhor abordagem no futuro.

Com o objetivo de avaliar a pertinência desta intervenção foi feita uma revisão narrativa da literatura. Recorrendo a vários motores de busca científica extraíram-se artigos científicos originais, revisões narrativas e sistemáticas e meta-analises, publicados a partir de 2018 (pré-pandemia).

Este artigo visa rever o impacto da pandemia COVID-19 em crianças e adolescentes diabéticos tipo 1, centrando-se nas suas complicações, taxa de hospitalizações e gestão de cuidados, procurando desenvolver, para o futuro, abordagens práticas que assegurem os melhores cuidados de saúde para todos os jovens afetados. Ter consciência do impacto e das principais barreiras na manutenção de um bom controlo da doença, de forma a ter uma melhor relação terapêutica e melhores resultados.

Palavras-chave: Diabetes tipo 1 em crianças; pandemia COVID-19; Cetoacidose diabética; Telemedicina; Confinamento

ABSTRACT

The global outbreak of SARS-CoV-2 (severe acute respiratory syndrome coronavirus) has been unique. Even before a detailed study of coronavirus disease 2019 (COVID-19) was conducted, substantial worries were expressed about the virus's potential impact on people with chronic diseases, such as type 1 diabetes.

Type 1 diabetes mellitus (T1DM) is an autoimmune disease defined by the death of insulin-producing beta cells in the pancreas, resulting in insulin insufficiency. It is one of the most common chronic diseases among children and adolescents, causing serious short-term consequences as well as a series of macrovascular or microvascular complications in later life. In children with diabetes, diabetic ketoacidosis remains the major cause of morbidity and death.

This review provides an overview of the current aspects of type 1 diabetes including its epidemiology, diagnosis, as well as a better knowledge about its management and therapy, and a short review of its main complications. It also provides additional information about the SARS-CoV-2 virus and an approach to the clinical picture of COVID-19 patients in order to learn and understand this pandemic better and to realize its impact on the overall population. Finally, with the ultimate aim of reporting and perceiving the challenges and concerns of the type 1 diabetes population during the covid-19 pandemic, there were discussed topics such as new-onset type 1 diabetes during the pandemic, the impact on glucose monitoring and telemedicine, type 1 diabetic patients with covid-19 and its severity and a brief review on the differences between lockdowns, with the purpose to draw some insights about a better future approach.

In order to assess the relevance of this paper, references were found as costume for narrative reviews of literature. Through a search of several databases, papers of various typologies were selected: original articles, systematic literature reviews, and meta-analysis. All concerned at least one of the debated topics and were published since 2018 (pre-pandemic).

This paper aims to review the impact of the COVID-19 pandemic in type 1 diabetic patients focusing on its complications, rate of hospitalizations, and management, looking to develop, for the future, practical approaches to ensure the best medical care of all youngsters affected. Being aware of the impact and the major barriers in the maintenance of great control of the disease, improving a better therapeutic relationship and better outcomes.

Keywords: Pediatric type 1 diabetes; COVID-19 pandemic; Diabetic Ketoacidosis; Telemedicine; Lockdown

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ABBREVIATIONS AND ACRONYMS

T1DM: Type 1 diabetes mellitus

DKA: diabetic ketoacidosis

COVID-19: coronavirus disease 2019

SARS-CoV-2: severe acute respiratory syndrome- coronavirus-2

ICA: cytoplasmic antibodies

IAA: antibodies to insulin

GAD65: glutamic acid decarboxylase

IA-2: phosphatase antibodies

ZnT8: zinc transporter8

HbA1c: glycated hemoglobin

GFR: glomerular filtration rate

TSH: thyroid-stimulating hormone

CSII: continuous subcutaneous insulin infusion

SMBG: self-monitoring of blood glucose

CGM: continuous glucose monitors

2019-nCoV: 2019 novel coronavirus

RNA: ribonucleic acid

WHO: World Health Organization

ARDS: acute respiratory syndrome

UK: United Kingdom

PCR: polymerase chain reaction

T2DM: type 2 diabetes mellitus

BMI: body mass index

ACE2: angiotensin-converting enzyme 2

ICU: intensive care unit

1. INTRODUCTION

Type 1 diabetes mellitus (T1DM) is an autoimmune disease defined by the death of insulin-producing beta cells in the pancreas, resulting in insulin insufficiency. It is one of the most common chronic diseases among children and adolescents, and it is still the most common type of diabetes in this age range. Its prevalence has been rising, especially among younger children. (1) It can cause serious short-term consequences, such as diabetic ketoacidosis and hypoglycemia, as well as a series of macrovascular or microvascular complications in later life. (2) Polyuria, polydipsia, and weight loss are common symptoms in children with type 1 diabetes.(3) The signs and symptoms usually develop quickly, and the prevalence of diabetic ketoacidosis (DKA) is primarily due to a delayed diagnosis.(1)

Since the outbreak of coronavirus disease 2019 (COVID-19), caused by the respiratory virus severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), in Wuhan, China, there has been a widespread alarm. (4) On January 30, 2020 (1), the World Health Organization designated the outbreak a Public Health Emergency of International Concern, and on March 11, 2020, it was declared a Pandemic. The global population's lifestyle has been altered tremendously, and individuals with a previous chronic illness, such as diabetes mellitus, are the ones who are suffering the most.(5) In many countries, the implementation of social distancing and stay-at-home orders or lockdown had a direct impact on how health care workers engaged with their patients in order to deliver normal care, which was especially difficult for pediatric T1DM patients.(6)

Given the high incidence of diabetes and its significant impact on COVID-19-related outcomes, it is critical to investigate and get the best available information to enhance patient outcomes in diabetic patients.(7)

The aim of this narrative review is to look into the vulnerability of type 1 diabetic patients during the COVID-19 Pandemic, as well as the most critical parts of their care. In this way, we will be able to draw some inferences about what the future holds for diabetics post-pandemic.

2. MATERIALS AND METHODS

The research used in this paper followed the methodology recommended for narrative reviews. The studies were based on type 1 diabetes mellitus in pediatric age during the pandemic of covid-19. The search focused on the difference in the new-onset type 1 diabetes before and after the pandemic, the care of patients during lockdown and the importance of telemedicine.

Papers of various typologies were selected: clinical cross-sectional, case-control studies, cohort studies, systematic literature reviews and meta-analysis, comprehensive reviews, time series analysis and original articles. Containing at least, one of the debated topics.

A literature search was conducted during the period of June 2021 to December 2021 using the following electronic search engines: PubMed, Google Scholar and Medscape.

The research aimed to find differences in type 1 diabetic children and adolescents two years before and during the actual pandemic, in which the following search terms were used either in the title, abstract, keywords or content: Type 1 Diabetes Mellitus" AND "COVID-19", "Type 1 Diabetes Mellitus" AND "Telemedicine", "Diabetic Ketoacidosis" AND "COVID-19".

Only articles dated between 2018-2021 and published in English or Portuguese were selected. In one specific article, an exception was made due to relative significance for this review although dating before 2018, related to a study of the prevalence of diabetic ketoacidosis.

During the selection of articles, the ones which considered individuals older than 17 years old were excluded, as well as articles that referred to type 2 diabetes mellitus.

After a critical analysis of the research, some articles were excluded after reading the title, the abstract or after their complete analysis for not addressing the theme of the work or for repeating information.

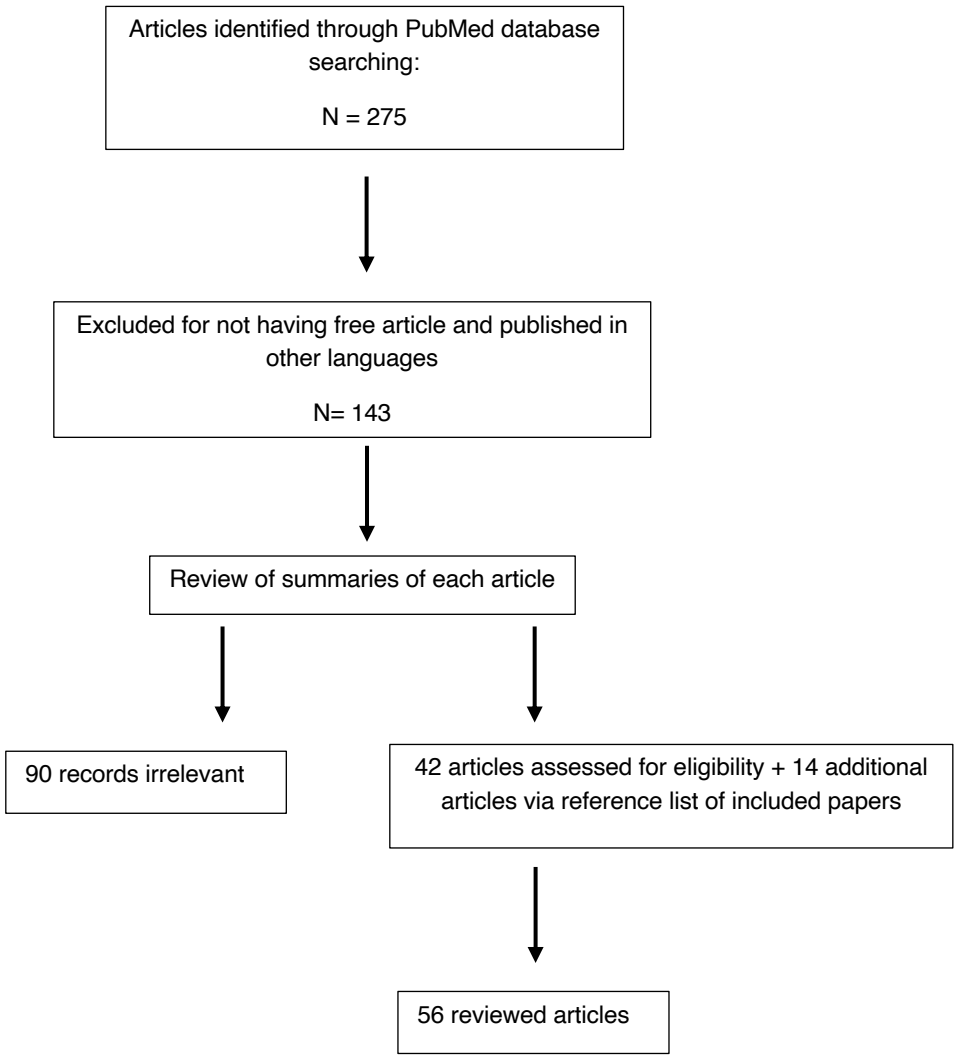

Diagram 1. Illustrating the method of research and selection of the revised articles.

3. RESULTS

3.1 Type 1 diabetes mellitus before Covid-19

3.1.1 Type 1 Diabetes Mellitus

Type 1 diabetes mellitus (T1DM) is an autoimmune disease in which insulin-producing pancreatic beta cells are destroyed. Beta cells autoantibodies are considered to form once a genetically vulnerable person is exposed to an unknown environmental element that causes a lack of immune control. The destruction of beta cells causes a reduction in insulin production, hyperglycemia, and clinical type 1 diabetes.(8)

The presence of circulating pancreatic autoantibodies suggests that the individual is at risk for or has developed T1DM. These antibodies include islet cell cytoplasmic antibodies (ICA), antibodies to insulin (IAA), glutamic acid decarboxylase (GAD65), insulinoma-associated 2, or protein tyrosine phosphatase antibodies (IA-2) and zinc transporter8 (ZnT8). The greater the number of detectable antibodies and the higher their titers, the greater the risk of developing T1DM.(1) A major amount of the genetic risk linked with type 1 diabetes is due to polymorphism in the HLA region. HLA DR4-DQ8 and HLA DR3-DQ2 are the HLA haplotypes with the highest risk. The risk for the heterozygote determined by these two haplotypes is much higher than for any of the homozygotes.(8)

Insulin is a necessary anabolic hormone that regulates glucose, lipid, protein, and mineral metabolism as well as growth. Insulin allows glucose to enter muscle and adipose cells, stimulates the liver to store glucose as glycogen and synthesis fatty acids, accelerates amino acid uptake, inhibits fat breakdown in adipose tissue, and stimulates potassium uptake into cells.(1)

3.1.2 Epidemiology

Globally, type 1 diabetes is increasing both in incidence and prevalence, with overall annual increases in the incidence of about 2–3% per year. (3)

The incidence of type 1 diabetes increases with age up to a peak around 10–14 years, but the disease can occur at any age. The incidence tends to be higher in boys than in girls in high–incidence countries, with the opposite pattern seen in low–incidence countries. After puberty, males tend to have an increasingly higher incidence of developing type 1 diabetes than females, even in low–incidence countries. In countries with a low incidence, the relative growth is the greatest. Most long-term incidence data focuses on children under the age of 15, with annual incidence ranging from 1 to 3 per 100 000 per year in China and other Asian and South American countries, around 10–20 per 100 000 in South European countries and the United States, and 30–60 per 100 000 in Scandinavia. Most countries have experienced non-linear fluctuations throughout time, with periods of low or no growth, such as Norway

from 2004 to 2012 and Finland from 2006 to 2011. During the years 2002–12, there was a modest increase in the number of cases in the United States. (8–10)

3.1.3 Diagnosis

A fasting blood glucose concentration of more than 126 mg/dl (7.0 mmol/L), a random blood glucose concentration of more than 200 mg/dl (111 mmol/L) plus symptoms, or an abnormal result from an oral glucose tolerance test are all used to diagnose diabetes. Abnormal glycemia must be present on two separate occasions in the absence of symptoms. A glycated hemoglobin (HbA1c) value of more than 6.5% (48 mmol/mol) can also be used to diagnose diabetes. HbA1c is less sensitive for diagnosis than fasting or stimulated blood glucose tests because glycemia progression can be quick in young patients with type 1 diabetes.(3,11)

Almost always, clinical history and a single capillary blood sugar measurement are enough to make the diagnosis. An impaired overall state of health, shortness of breath, abdominal pain, or vomiting are examples of other clinical signs. Diabetes was once misdiagnosed as asthma (because of *Kussmaul* respiration) or possibly appendicitis; but, in today's era of speedy laboratory testing, such errors should not be made.(12)

Children with type 1 diabetes commonly present with symptoms of polyuria, polydipsia, and weight loss; approximately a third present with diabetic ketoacidosis.(11)

Additional laboratory tests, such as diabetes-associated antibodies, can be performed if there is doubt, but they are not required for the initial diagnosis and should be left to specialized diabetes treatment centers for differential diagnostic study.(12)

Over 90% of people with newly diagnosed type 1 diabetes have measurable antibodies against specific β-cell proteins, including insulin, glutamate decarboxylase, islet antigen 2, zinc transporter 8, and tetraspanin-7. (3)

On the day of presentation, a child with a suspected initial presentation of diabetes mellitus should be evaluated by a diabetes specialist or in a hospital emergency room. As soon as the diagnosis is made, the patient should be transferred to a diabetes team with experience treating children. (12)

3.1.4 Management

It is important to collect a proper clinical, surgical, social, and family history at the initial outpatient appointment. Clinicians should take measurements of their patient’s height, weight, and blood pressure. Patients with T1DM are more likely to develop autoimmune thyroid disease, therefore the thyroid should be palpated. The skin should be checked, especially where insulin is injected or infused. (1)

For patients with long-term T1DM, it is important to evaluate pedal pulses, foot abnormalities, pre-ulcerative lesions, ulcerations, callus, and onychomycosis during a foot exam. To rule out peripheral neuropathy, a 10-g monofilament exam should be used to examine vibratory and protective sensitivity.(1)

Every 3 to 6 months, HbA1c should be checked. HbA1c is a measure of glycemic control during the past two to three months.(1) An annual lipid profile, liver function tests, urine albumin to creatinine ratio, serum creatinine, GFR, and TSH should all be performed. If the prior findings were abnormal, these tests might be done more regularly. It's also worth noting that people with T1DM are more likely to acquire additional autoimmune disorders such as autoimmune thyroid disease, primary adrenal insufficiency, celiac disease, and vitiligo. When appropriate, screening for these illnesses should be considered.(1,13,14)

a. Insulin therapy

Insulin therapy is the fundamental element of type 1 diabetes medical treatment. Insulin replacement treatment aims to match physiological insulin production patterns as closely as possible. Because plasma insulin levels naturally vary throughout the day, with low levels during fasting and nighttime periods and high spikes during the postprandial period, combinations of short and long-acting insulin preparations are frequently employed to mimic these patterns.(13)

The age of the children, the duration of diabetes, the family's lifestyle, school support, socioeconomic considerations, and family, patient, and physician preferences all play a role in determining the insulin regimen. All children should be treated to fulfill glycemic objectives, regardless of the insulin regimen they are on. (14)

The honeymoon period, due to the production of insulin by the residual beta cells of pancreatic tissue, can last two years after the diagnosis and is defined by the control of the disease and low insulin requirements. After that, to maintain glycemic objectives, more intense management may be required.(14)

Basal-bolus regimens (long-acting basal insulin analogs and rapid-acting bolus insulin analogs) and continuous subcutaneous insulin infusion (CSII) treatment have both been used to manage strict diabetic control.(14,15) Insulin dose must be adjusted often to account for consumed carbohydrates, glucose levels, physical activity, and illness or stress.(3) CSII is the most physiological form of treatment, that is, the one that best mimics insulin secretion by the pancreas and should be preferred for the treatment of DM1 in pediatric age.

b. Glucose monitoring

The current gold standard for metabolic monitoring is self-monitoring of blood glucose (SMBG).(12) Routine SMBG is required for determining immediate insulin doses and its safety and adjusting insulin dose regimens over time based on blood glucose patterns and trends.(13) There is a link between getting multiple SMBGs and having a lower HbA1C in persons with type 1 diabetes. The frequency and timing of SMBG should be determined by the patient's requirements and goals.(16)

For persons with T1DM, continuous glucose monitors (CGM) are incredibly important instruments. CGM uses a subcutaneous sensor to detect the interstitial glucose levels every 3–5 minutes and send the data to a reading device. It allows the detection of asymptomatic hypoglycemia and hyperglycemia. (1,12,14) More and more, CGM is being used instead of self-monitoring capillary blood glucose.

Across all pediatric age groups, an HbA1C target of <7.5 percent (58 mmol/mol) is advised. Children with frequent hypoglycemia or hypoglycemia unawareness must have their blood glucose targets adjusted. Individual objectives should be set, and lower targets may be justified based on a benefit-risk analysis. (17)

c. Education

In children with new-onset diabetes, intensive diabetes education is needed to help them manage their condition. This team should include a pediatric endocrinologist, a nurse, a pediatrician, a dietitian, a social worker, and mental health professional.(14)

Diabetic treatment during childhood and adolescence imposes significant difficulties on the children and their families, demanding frequent assessments of psychosocial state and diabetes distress during diabetes consultations.(17)

The action of insulin, how to administer and adjust dosage; monitor blood sugar and ketones; sick leave management and prevention of diabetic ketoacidosis (DKA); nutritional therapy; physical activity; and the prevention, detection, and treatment of hypoglycemia are all topics that need to be covered. (14)

3.1.5 Complications

Despite advances in the management of the disease, complications still exist, and some can be potentially fatal. Hypoglycemia and diabetic ketoacidosis are common and life-threatening acute complications.(12)

Regarding long-term complications, both microvascular and macrovascular complications are common in both types of diabetes (type 1 and type 2). Hyperglycemia is the key risk factor for microvascular disease (Table 1), and lowering HbA1c, especially early in the illness, is linked to reductions in microvascular disease incidence and progression. On the other hand, in macrovascular complications (Table 1), intensive blood sugar management does not appear to have the same effect. (3,12)

Table 1. Microvascular and Macrovascular Complications

Microvascular Complications (3,14)		**Macrovascular Complications** (3,14)
Retinopathy	An initial dilated and comprehensive eye examination is recommended at age 10 years or after puberty has started	Atherosclerosis
Neuropathy	Children ≥15 years with poor metabolic control should be screened yearly after 5 years of type 1 diabetes	Thrombosis
Nefropathy	After 5 years of diabetes diagnosis, annual albuminuria screening using a random spot urine sample for albumin-to-creatinine ratio should be considered at puberty or at age >10 years, whichever comes first.	

a. Hypoglycemia

Hypoglycemia is a key barrier for children with type 1 diabetes, and it can create difficulties for them to meet their glycemic goals. The use of CGM on a regular basis in a clinical context may help to decrease hypoglycemic episodes, as well as the duration of them.(14) Children who have experienced a severe hypoglycemia episode in the previous 12 months, as well as immigrant children, are more vulnerable.(12) When having severe hypoglycemia, children must be treated at home with glucagon or in the hospital with intravenous dextrose. (14)

b. Diabetic Ketoacidosis

Diabetic ketoacidosis (DKA), a metabolic disorder defined by the triad of hyperglycemia, acidosis, and ketosis, affects 30 to 50 percent of children diagnosed with T1DM. (18) In children with diabetes, DKA remains the major cause of morbidity and death.(14)

DKA is caused by an increase in counter-regulatory hormones and a reduction in effective circulating insulin. (19) According to The SEARCH study, the prevalence of type 1 diabetes among youth did not change significantly over time, with 30.2 % in 2002–2003, 29.1 % in 2004–2005, and 31.1 % in 2008–2010. The overall prevalence was highest (39%) in the 0- to 4-year age group and lowest (23%) in the 15- to 19-year age group. Within each age group, no variations in DKA at onset were noted over time.(20)

DKA can be avoided by recognizing it early and starting insulin treatment. (14) In DKA, adequate fluid replacement is the most critical first therapeutic measure, followed by insulin delivery. (19)

3.2 COVID-19 Pandemic

3.2.1 COVID-19

Coronaviruses are encapsulated non-segmented positive-sense RNA viruses that are found in humans and other animals. They belong to the family *Coronaviridae* and the order *Nidovirales.*

A series of pneumonia cases of unknown source appeared in Wuhan, China, in December 2019, with clinical presentations that were similar to viral pneumonia. Sequencing of material from the lower respiratory tract revealed a new coronavirus, which has been called the 2019 novel coronavirus (2019-nCoV).(21) As an RNA virus, 2019-nCoV has a high mutation rate. This feature gives this newly introduced virus the opportunity to evolve and become more effectively spread from person to person, as well as potentially more virulent. (22)

The virus, caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), spread quickly over the world, killing millions of people. On January 30, 2020, the World Health Organization labeled the outbreak a Public Health Emergency of International Concern, and on March 11, 2020, a pandemic was declared. (6,23)

Since then, governments and public health officials all around the globe have made extraordinary precautions to prevent the virus from spreading. Almost every country has put in place strong precautions: countrywide lockdowns, in which internal travel was restricted and borders were blocked, are some of them.(5,24)

According to WHO- World Health Organization until the day of 17 December 2021 there were 271 963 258 confirmed cases and 5 331 019 confirmed deaths worldwide.

3.2.2 Clinical picture

The infection's clinical picture is quite variable, ranging from asymptomatic people to moderate forms with fever, cough, weakness, and loss of smell and taste, to severe cases requiring admission to

the intensive care unit for acute respiratory distress syndrome (ARDS).(23) Serious sickness is more probable to occur in the elderly and those with underlying medical disorders such as cardiovascular disease, diabetes, chronic respiratory disease, or cancer.

When an infected person coughs, sneezes, speaks, sings, or breathes, the virus spreads in microscopic liquid particles from their mouth or nose. Larger respiratory droplets to smaller aerosols are among the particles.

3.3. Type 1 Diabetes Mellitus during COVID-19 Pandemic

3.3.1 New-onset Type 1 Diabetes Mellitus

Except in children with comorbidities, COVID-19 has had a minor influence on the pediatric population. Children who acquire non-COVID-19 diseases during the pandemic, on the other hand, are in danger of deteriorating or dying owing to a lack of hospital treatment. Children with type 1 diabetes, in particular, may advance quickly to diabetic ketoacidosis if insulin administration is delayed, putting them at risk for increased morbidity and death.(25)

Some studies focused on whether COVID-19 had any effect on the first diagnosis of T1DM in children. It is generally established that new-onset T1DM has a seasonal fluctuation, with more cases occurring in the fall and winter when viral exposure is higher.(6)

DKA is a frequent and possibly fatal acute onset diabetic condition caused by a relative or absolute insulin shortage. DKA can develop at any time, including during the start of the disease, when the patient misses insulin doses, or when the patient is suffering from another mild to severe sickness.(23)

In the first two months of the pandemic in Italy (February 2020 to April 2020), the Diabetes Study Group of the Italian Society for Pediatric Endocrinology and Diabetes explored whether COVID-19 affected children with new-onset and existing type 1 diabetes. There were 23% fewer new diabetes cases throughout the observation period compared to the same period in 2019 (February 2019 to April 2019), and children presenting with DKA in 2020 had more severe DKA (pH <7.1 and bicarbonate <5 mmol/L) than in 2019 (44.3 percent vs. 36 percent, respectively;) (26)

As well as this, a study from Germany analyzed data of 532 children and adolescents with new-onset T1DM from March 13 to May 13, 2020. DKA was present in 44,7% of patients and severe DKA in 19,4 %. The frequency of DKA was higher compared with the 2 previous years (44,7 percent in 2020; 24,5 percent in 2019 and 24,1 percent in 2018). The incidence of severe DKA was also higher compared with the two last years. During the COVID-19 pandemic, children under the age of six had the highest risk of diabetic ketoacidosis (51.9 percent in 2020 versus 18.4 percent in 2019;) and severe diabetic ketoacidosis (24.4 percent in 2020 vs 12.2 percent in 2019). (27)

On the other hand, a multicenter study in the United Kingdom (UK) including 30 pediatric patients from 5 inpatients units from 23 March to 4 June 2020 (coinciding with the U.K. Government lockdown) found an estimated increase of 80 percent in the incidence of new cases of T1DM compared to prior years. With ten cases apiece, there appears to be a rise in just two inpatients units. The remaining three units had comparable rates to the prior year.

Most patients with new-onset T1DM (70%) developed DKA, with 52 percent having severe DKA (pH 6.82–7.05). 21 individuals were tested for SARS-CoV-2, and three of the five patients who tested positive had severe DKA with persistent hypokalemia, and one PCR positive child had a hypokalemia-related cardiac arrest but recovered totally.(28)

An observational retrospective cohort research involving young T1DM patients from Bucharest's Marie Curie Emergency Children's Hospital study children diagnosed during March 2020–February 2021. The number of new T1DM cases in March and April 2020 was lower than in the same months in 2018 and 2019. The monthly number of new T1DM cases was greater between May 2020 and February 2021, with a mean of 13.2 recent cases per month, this compares to a mean of 9.4 cases per month during the previous two years. During the pandemic, the proportion of people having DKA at the start of the illness grew to 67.40 percent. (29)

COVID-19's effect on the incidence of pediatric T1DM was also explored in a German investigation. Patients diagnosed with T1DM between March 13 and May 13 of each year from 2011 through 2020 were included in this study. The study shows that there was no substantial rise in the incidence of pediatric T1DM children in Germany during the COVID-19 pandemic, which is consistent with the study in Italy but not in the one in the UK and Bucharest. (30)

Other investigations have reported an extremely high number of children and young people presenting with diabetic ketoacidosis during the early months of the pandemic and these findings are consistent with them. (25,31–33) Concerning to incidence of new cases of T1DM, the data is not so consistent, with a decrease in the number of new cases and (25), as well, a rate comparable to previous years was observed. (32,33)

3.3.1 Type 1 Diabetes Mellitus management during lockdown

The imposition of social distance and lockdown during the COVID-19 pandemic had a direct influence on how health care practitioners dealt with their patients to deliver normal treatment.(6) People with T1DM were unable to continue with their usual follow-up and were forced to change their chronic illness care.(23) Despite this abrupt adjustment in lifestyle, all research to date suggests that people with T1DM did not experience a worsening of their glucose control during the lockdown.(4,23,34–37)

Italian research looked at changes in glycemic control three weeks before and after the lockdown was established. Between November 2019 to February 2020 and February 2020 to May 2020

they studied a total of 62 pediatric patients with T1DM who used a CGM device (Dexom G6 CGM). According to Predieri B et al, the average time that glucose levels were in the reference interval increased significantly (60.5 percent to 63.5 percent), while the time that glucose levels were above the reference interval and below the reference interval decreased significantly (37.3 percent to 34.1 percent; 1.85 to 1.45 percent respectively).(37)

a. Telemedicine

Telemedicine has taken center stage in medical treatment. During this situation, it has appeared as a tool for patients to receive care while maintaining social distance and reducing the risk of viral transmission.(38)

Patients can conduct physician visits from the convenience of their own homes. This is especially good for youngsters and people who are anxious in medical circumstances. (38) Using video conferencing and other similar technologies for school and college classes around the same time period ensured that parents and children were familiar with it, which helped make it an easy platform to use.(39)

Many juvenile T1DM patients use intelligent diabetic equipment such as continuous subcutaneous insulin infusion pumps and continuous glucose monitoring. Both employ Web-based administration software to gather and store data that can be shared between patients and their health care team members.(6)

Telemedicine has proven to be a strong resource for the control of type 1 diabetes throughout the pandemic. Good glycemic control during these months of lockdown has been proof that this help has become essential in the care of these patients.

3.3.3 COVID-19 in patients with Type 1 Diabetes Mellitus

Diabetes has been recognized as a risk factor for poor COVID-19 disease outcomes, such as progression to acute respiratory distress syndrome (ARDS) and death. (7) Concerns have been raised regarding whether COVID-19 might cause severe illness to children with T1DM as well. (6)

COVID-19 symptoms in patients with type 1 diabetes are often the same as in the general population: dry cough, nausea, vomiting, and fever. The infection may be associated with hyperglycemia and diabetic ketoacidosis at first. Some of the common COVID-19 symptoms (nausea/vomiting) may disguise the development of DKA, delaying diagnosis and worsening the outcome.(40,41)

There is currently no suggestion that young people with type 1 diabetes have a greater rate of mortality or morbidity, including the risk of hospitalization, compared to their healthy peers.(6,26,40,42,43)

According to a large multicenter European investigation on COVID-19, which included 582 people with PCR-confirmed SARS-CoV-2 infection, there were no occurrences in children and adolescents with preexisting diabetes. (44)

A report based on the experience from pediatric practices in China, Italy, Spain, and United States suggests that until 31 august 2020 youths with diabetes < 25 years of age were not at an increased risk for hospitalization due to COVID-19. (42)

The CORONADO research was to describe the phenotypic features and prognosis of diabetic patients hospitalized with COVID-19 in 68 French hospitals between March 10 and April 10, 2020. It showed that compared to individuals without type 1 diabetes, older patients with COVID-19 and type 1 diabetes had a greater death rate. The risk of type 1 diabetes in younger people was lower. COVID-19 severity proved to be less severe in T1DM patients than in T2DM patients, with half the probability of mortality. The younger group had a lower severity, which is mostly attributable to a decreased rate of tracheal intubation.(45)

Other variables appear to exacerbate COVID-19 concerns in people with type 1 diabetes, such as glycemic control, BMI, race, hypertension, microvascular and macrovascular complications. (46–48)

3.3.4 First wave 2020 vs second wave 2021

Most of the studies done to date are related to the first wave of the 2020 pandemic. Given the large dimension that the pandemic has taken, it was important to understand if there were changes from the 2020 containment to the 2021 containment.

For example, the first wave in India was not as extensive: the disease dissemination was restricted, and the severity of illness in T1DM patients could not be assessed due to the small number of patients. In contrast, the COVID-19 second wave has become a huge health concern. In the second wave of COVID-19 in India, they found no significant increase in the severity of COVID-19 in children with T1DM, even though many of their relatives were impacted.(49)

4 DISCUSSION

The COVID-19 pandemic has brought several healthcare issues, one of which is the management of chronic illnesses such as diabetes mellitus.(39) Because of the nature of their condition, patients with type 1 diabetes require more regular monitoring, follow-up, and attention to insulin dosage change to achieve the best results.(39)

4.1 DKA in New-onset T1DM

The pandemic is a time of great uncertainty and rapid change to clinical services and public health messaging. (31)

The data regarding the incidence rate of new-onset T1DM were disparate. Thus, an analysis is needed. Overall, the first two months of lockdown (March and April) saw a decrease in the number of new cases. (25,26,29,30) In the early weeks of the pandemic, people were only permitted to leave the house for a few clearly specified purposes, including as required medical assistance and grocery shopping. As a result, children's lifestyles changed dramatically, resulting in much lower seasonal exposure to common infectious microorganisms, which may have contributed to a drop in new T1DM cases during the pandemic. (6,29) Likewise, several data showed that there weren't significant changes in this rate compared with the previous years. (30,32,33) Indeed, some studies still managed to show some increase, especially in the months following the lockdown ones. (28,29) The physiopathological factors that may contribute to the rise in T1DM cases are not yet fully understood but some hypotheses may arise.(29) Firstly, after the regulations of the first few months of confinement, which came about rapidly and abruptly, people ultimately began to start going out more often, and consequently being exposed to more microorganisms. Furthermore, following a period of severe limitation in seeking medical treatment, some new cases that could have been diagnosed earlier ended up decompensating with DKA, and the need for medical care finally grew. There might still be a link between COVID-19 and T1DM. COVID-19 has been shown to cause acute onset diabetes and DKA in a few people, simulating T1DM. (50)

The UK study that demonstrates an increase in the new diagnosis of T1DM can be explained by this and, additionally, a lack of sample (only 2 of the 5 inpatients units) may not be sufficient to draw conclusions. Furthermore, there was no indication that the rise in new T1DM cases was statistically significant or associated with SARS-CoV-2 infection.(6)

The observed increase in the number of patients with new-onset T1DM with DKA and severe DKA during the COVID-19 pandemic could be explained by the decreased availability to primary care services and parental fear about presenting to healthcare professionals, which together contributed to a delay in diabetes diagnosis in children, resulting in more severe DKA in various countries. (6) (49) In addition, based on data that other coronaviruses bind to ACE2 receptors produced by beta cells, there

has also been speculation that COVID-19 infection may cause ketoacidosis by causing direct damage to pancreatic beta cells.(51)

4.2 Management

Despite this sudden adjustment in lifestyle, studies suggest that people with T1DM did not experience a worsening of their glucose control during the lockdown.(23)

Medical activities were frequently restricted to near-zero levels in order to increase ICU capacity and limit social activities among individuals unless absolutely essential. If it hadn't been for telemedicine, those with chronic illnesses would have been deprived of their follow-up check-ups.(23)

Some authors emphasized that slowing down normal tasks had a positive influence on glucose management. This is most likely related to a more regular lifestyle, more time spent preparing meals, and more risk awareness of more serious COVID-19 consequences.(52) In particular, parents were forced to stay at home so had more time to cope with the condition and the family environment may be more attentive in diabetes care.(53) This way, they can measure their children's glycemic levels more frequently, adjust their insulin management, and prepare meals more precisely.(23) Whilst, with the help of new technologies such as CGM and CSII, it was possible to maintain a more natural control of blood glucose levels.

Additionally, psychological responses to a prolonged pandemic situation may have an impact on glycemic control: Depression and anxiety disorders may be confounding variables throughout this era.(54) This feature emphasizes the importance of psychological screening for adolescents with T1DM in order to prevent not only psychological issues but also diabetic complications, especially during stressful occasions like this. (54)

After the pandemic, telemedicine could provide a chance to give more touchpoints for the most at-risk diabetics as well as provide more clinical treatment without demanding further physical clinical areas.(40)

4.3 T1DM with COVID-19

It is fundamental to learn more about the reasons that led to reduced rates of hospitalization among children with T1DM during the COVID-19 pandemic.(6)

Firstly, T1DM is more frequent in younger people, while older patients with COVID-19 had greater rates of hospitalization and death. (6) Thereafter, patients with a history of T1DM are given a lot of information on how to manage their diabetes while they're sick. These recommendations give significant tools to help patients avoid hospitalization. (6) Furthermore, stay-at-home orders and school closures

are likely to have increased patient and caregiver participation in diabetes control at home, this may have helped to reduce emergency department visits and hospitalizations. (6)

COVID-19 has a wide range of clinical manifestations. Fever, cough, and hypo/hyperglycemia were the most often reported symptoms. Shortness of breath, headache, myalgia, upper respiratory symptoms (such as sore throat and rhinorrhea), and gastrointestinal symptoms (such as nausea and diarrhea) are all possible side effects. (55) T1DM patients' manifestations have been described as the same as the general population like nausea, vomiting, fever, and dry cough. (56) Potential hypoglycemic or hyperglycemic episodes resulting from severe illness should be avoided and the prevention of DKA should be the most priority.

Higher severity of illness and mortality rate were described in adults with T1DM, especially if they have cardiovascular complications, higher HbA1c level, higher body mass index, and non-Hispanic race. (55)

Currently, the general public's health advice and patients with type 1 diabetes throughout the pandemic is the same: wear masks, maintain social distancing guidelines, avoid unnecessary travel, and avoid indoor events as much as possible.(40) As well as, maintaining great glycemic control.

4.4 Lockdown changes

Although we still have a few data regarding the differences between the major confinements to which this pandemic has already subjected the worldwide population, in general, we can find that there were no major differences from one lockdown to another.

Despite being a major means of transmission, children have been little affected by this virus. And this is not an exception for children with type 1 diabetes.

With the prolonged time of the pandemic, glycemic control may be compromised, so it is important that in the future, the constant follow-ups and visits to the physician continue, with considerable help from telemedicine endorsed with the use of new technologies like CSII and CGM.

5 CONCLUSION

By way of conclusion, the COVID-19 pandemic had a major impact on type 1 diabetes.

During the COVID-19 outbreak, a large number of children obtained a delayed diagnosis, which changed the way type T1DM was presented. Patients with newly diagnosed diabetes have appeared with DKA and several times with a more severe DKA. Specific measures are needed in the future to educate and reassure parents about the need for timely attendance at the emergency unit for children with symptoms unrelated to COVID-19.

The majority of T1DM patients who had COVID-19 had a minor illness or were asymptomatic, much like their peers without diabetes. Children with T1DM and COVID-19 exhibited significantly lower disease severity than adults with diabetes and COVID-19.

Even though children are less susceptible and have a milder illness course, children with comorbidities may be at a higher risk of consequences.

Despite the limits of lockdown, T1DM patients' glycemic control improved. These findings imply that allowing more time to manage diabetes, and employing the latest technologies developed for the management and treatment of the disease, helps achieve better glycemic control.

Teleconsultation and video conferencing played a key role in maintaining optimum healthcare delivery to patients with T1DM during the COVID-19 pandemic. Some of these techniques can be employed even after the outbreak has passed to increase patient convenience and minimize hospital outpatient burden.

Ultimately, greater study into the immediate and long-term effects of COVID-19 on people with type 1 diabetes is required.

During this unprecedented pandemic, it is critical to continue to study and report on the outcomes of people with type 1 diabetes, so that the public health recommendations are based on the highest available quality data.

6 TAKE-HOME MESSAGES

1. Pediatric patients with T1DM do not become severely sick with COVID-19, conversely adults with T1DM or T2DM and COVID-19.

2. Postponements in receiving medical care contributed to an increase in the incidence of severe DKA among juvenile patients with newly diagnosed T1DM during the lockdown.

3. The lockdown resulted in a surprising improvement in glycemic control in young T1DM patients diagnosed previously to Pandemic.

4. In the future, specific steps will be needed to educate and reassure parents about the importance of prompt emergency room attendance for children with symptoms unrelated to COVID-19.

5. It is also important to develop measures to guarantee scheduled appointments for patients who have non- COVID-19 diseases more efficiently in the pediatric emergency department.

6. During the COVID-19 pandemic, the use of remote technologies and telemedicine in children with diabetes improved glycemic control.

7. Lessons learned from the COVID-19 pandemic in diabetes management should benefit in delivering better treatment for young T1DM patients and improving their health outcomes.

8. For children with symptoms unrelated to COVID-19, specific initiatives are needed to educate and reassure parents about the significance of immediate hospital attendance.

9. Although children with T1DM affected with SARS-COV-2 virus have a minor disease, they are still a major way to spread the virus. Social distancing measures and hygiene etiquette should be instilled in all children.

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