REVIEW

Covid-19 infection in children and adolescents and its association with type 1 diabetes mellitus (T1d) presentation and management

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Abstract

Children seem to be affected by the new SARS-CoV-2 virus less severely than adults, with better prognosis and low mortality. Serious complications of COVID-19 infection in children include multisystem inflammatory response syndrome in COVID-19 infection (MIS-C), myo-or pericarditis and, less frequently, long COVID syndrome. On the other hand, adults with type 1 (T1D) or type 2 diabetes (T2D) are among the most vulnerable groups affected by COVID-19, with increased morbidity and mortality. Moreover, an association of SARS-CoV-2 with diabetes has been observed, possibly affecting the frequency and severity of the first clinical presentation of T1D or T2D, as well as the development of acute diabetes after COVID-19 infection. The present review summarizes the current data on the incidence of T1D among children and adolescents during the COVID-19 pandemic, as well as its severity. Moreover, it reports on the types of newly diagnosed diabetes after COVID infection and the possible pathogenetic mechanisms. Additionally, this study presents current data on the effect of SARS-CoV-2 on diabetes control in patients with known T1D and on the severity of clinical presentation of COVID infection in these patients. Finally, this review discusses the necessity of immunization against COVID 19 in children and adolescents with T1D.

Keywords COVID-19 · Diabetes · Children · Epidemiology · Pathogenesis · Complications

Introduction

In December 2019 a novel infectious disease was identified in Wuhan, China, caused by a new coronavirus, which was named SARS-CoV-2. Ever since, the disease has spread throughout the world, and in March 2020 the World Health Organization (WHO) officially declared the Covid-19 Pandemic [1]. Although the disease presents mainly with respiratory symptoms, all systems of the human body can potentially be affected [1]. Countries all over the world took drastic measures to prevent the spread of the virus such as: hygiene measures (protective masks, keeping distances, hand washing on a regular basis), molecular and antigen diagnostic tests, detection of antibodies against the virus, quarantine and isolation at home, temporary lockdown of stores, schools and public services and most importantly vaccination against the virus. Despite the effect of the aforementioned measures on controlling the new pandemic, the disease continues to present in waves with variable severity and impact on humanity [2].

Although children and adolescents have been relatively spared by COVID-19 compared to adults, high-risk groups at risk of severe infection have been identified and pediatric complications, including MIS-C, myocardiac involvement, and long COVID syndrome have been observed [3]. Adults in general are more severely affected by COVID infection; this is particularly true for adult patients with diabetes of any type, obesity, metabolic syndrome (hypertension, dyslipidemia, impaired glucose metabolism), smoking, and other chronic conditions who are at increased risk of hospitalization and ICU admission, and have increased mortality rates [4].

SARS-CoV-2 has been reported to specifically bind to pancreatic β-cells, among other tissues, and to affect the development of new cases of diabetes (acute diabetes) or to accelerate the development of T1D or T2D [5]. There are conflicting results, however on the effect of COVID-19

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pandemic on the incidence of newly diagnosed T1D, or acute DM in childhood. Moreover, there are limited data on the impact of COVID infection in children with known T1D, in terms on their glycemic control or the severity of COVID infection. Thus, to bridge these gaps the aims of the current review were to: 1. report on the incidence and severity of T1D among children and adolescents during the COVID-19 pandemic, 2. explore the types of newly diagnosed diabetes after COVID-19 infection and the possible underlying pathogenetic mechanisms, 3. describe the effect of the pandemic on diabetes control and on the severity of clinical presentation of COVID-19 infection in children and adolescents with known T1D, and finally, 4. highlight the necessity of immunization against COVID 19 in children and adolescents with T1D.

Methods

A literature search on three databases (PubMed, Google Scholar and Scopus) was conducted by two researchers independently. Keywords used were: "Diabetes mellitus type 1, pediatric, child, adolescent, COVID-19, SARS-CoV-2, epidemiology, pathogenesis, complications, pediatric diabetes, adults". Limitations included: a. articles in

English, b. patients aged 0–18 years, c. approved treatment for pediatric T2D, d. publication date between 01/01/2020-31/08/2022. Duplicates and pertinence were deemed according to title and abstract if available. Full-text articles for all relevant studies were reviewed. Following independent revision, the researchers met to resolve disagreement by discussion. In the absence of consensus, a third researcher would review the article.

Results

Literature search was performed in three stages (Table 1). A. Initially articles that were studying the epidemiology and complications of children and adolescents without diabetes and COVID-19, were searched in the databases. Of the 46 articles found, 25 articles were excluded (2 were duplicates and 23 were excluded by title and abstract) and 21 remained. B. Secondly, articles on children and adolescents with diabetes and COVID-19, epidemiology and complications were searched in the databases. Of the 56 articles found, 2 were excluded by abstract and title and 54 remained. C. Finally articles on adults with diabetes and COVID-19, epidemiology and complications were searched in the databases. Of the 36 articles found, 5 were excluded

Table 1 Prisma Flow diagram

A. Children and adolescents without diabetes   **B. Children and adolescents with diabetes**   **C. Adults with diabetes**
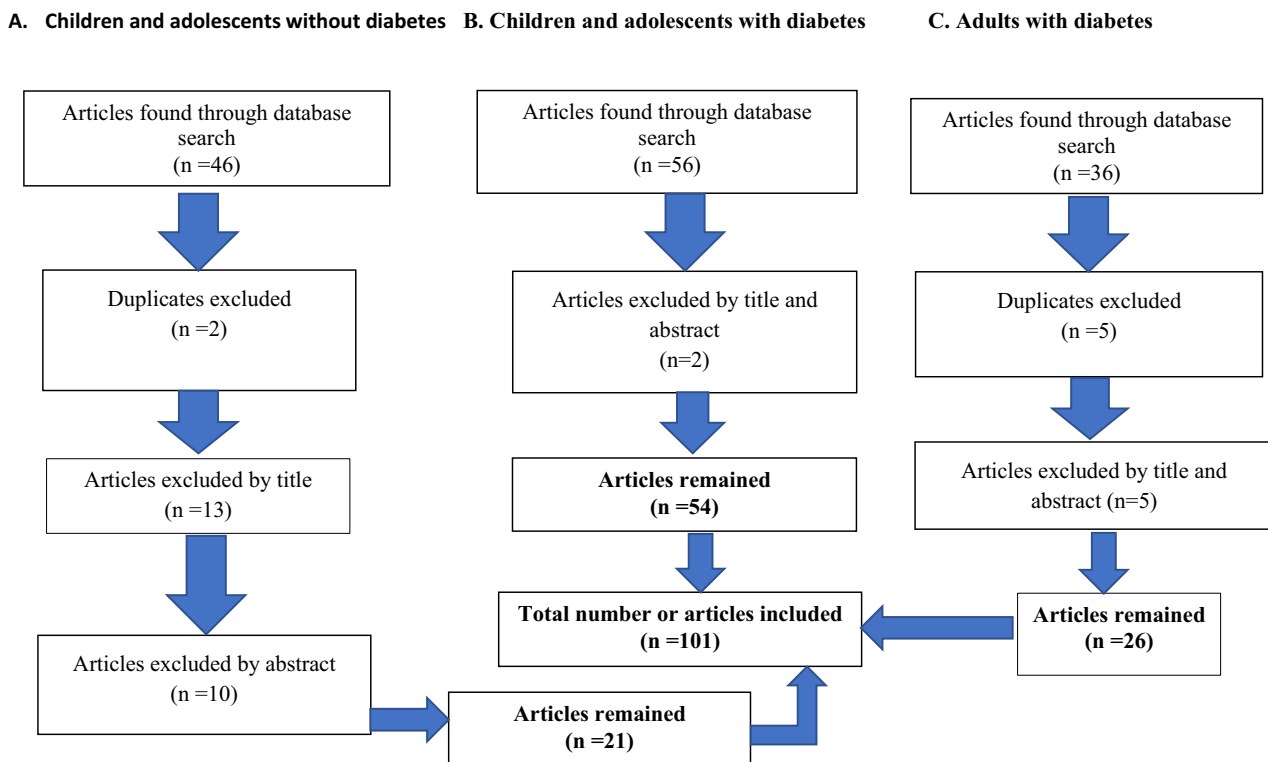
by abstract and title and 5 were duplicates; thus 26 remained. In total 101 articles were included in the references. After consideration, the two researchers agreed on the use of a total of the above 101 articles.

Covid-19 infection in children and adolechents

1a) Clinical presentation of COVID-19 infection in childhood

Children and adults share the same possibility to be infected with COVID-19 [6]. Disease transmission in childhood usually occurs within the family or at school, while vertical transmission is rare [7, 8].

Many children remain asymptomatic, and as a group, even when symptomatic, they exhibit milder symptoms, shorter disease duration and better prognosis than adults. Children usually present similarly to adults with symptoms such as fever, rhinitis, fatigue, headache, muscle aches, as well as lower respiratory tract and gastrointestinal symptoms [9]. The commonest symptoms appear at a lower frequency than adults, i.e., fever (56% vs 71%), cough (54% vs 80%) headache (28% vs 58%), diarrhea (13% vs 31%) [10]. The clinical presentation of COVID-19 symptoms in childhood and its severity varies by age group. Among neonates, 12% have been reported to present in severe clinical condition and 40% of them with dyspnea. Among infants aged <12 months, 42.5% present with mild clinical symptoms, 39.6% moderate and 10.6% severe, with 2% of them treated in the ICU (death in 0.08%). Children older than one year of age and adolescents present with fever (51.6%), lower respiratory tract symptoms, i.e., cough (48.5%), pneumonia (64.9%), while severe clinical condition presents less frequently (2.5%) than infants, with 0.2% cases treated in the ICU and 1 reported death [9, 11].

A multicenter study from 82 hospitals in 25 European countries, including 582 children with COVID-19 infection, reported the absence of lower respiratory symptoms in 87% of children, the necessity for hospitalization in 62%, intensive care unit (ICU) treatment in 8% with a median patient age of 5 years, and the use of mechanical ventilation only in 4% of patients for a mean duration of 7 days [12].

Risk factors for ICU admission include: a) Age <1 month, b) male sex c) preexisting lower respiratory symptoms on admission [13].

1b) Risk factors for severe COVID-19 infection in children

Infants are at greatest risk for severe COVID-19 infection, with the respiratory system being mainly affected. This is

Table 2 Risk factors for severe COVID-19 infection in children and adolescents (Sinaei et al 2020) [13]

- Age (<1 year). Race and ethnicity (Africans and Hispanic)-> Increased risk of P-ARDS
- Underlying diseases (congenital heart diseases, neurologic, genetic, metabolic)
  - ▓ Diabetes Mellitus type 1 and 2, obesity
  - ▓ Hypertension, cardiovascular diseases
  - ▓ Immunodeficiencies, immunosuppression, malignancy
  - ▓ Chronic respiratory diseases (cystic fibrosis, severe asthma)
  - ▓ Chronic hematologic disorders (thalassemia, sickle cell disease)
  - ▓ Chronic hepatic disease
- Pregnancy, smoking (incl. passive)

Key to Table 2:
P-ARDS pediatric acute respiratory distress syndrome, *Incl* including

attributed to the fact that infants have narrower airways, and at the same time the immune system is still immature; moreover, they may have a lower gene expression of the angiotensin converting enzyme-2 (ACE2) receptors [14]. There are also ethnic differences regarding the risk for severe respiratory system involvement from COVID-19. African and Hispanic populations are at greatest risk for acute respiratory distress syndrome. Children and adolescents with T1D, obesity, hypertension, immunodeficiencies, malignancies, chronic respiratory diseases (cystic fibrosis, severe asthma etc), and other chronic diseases are more susceptible to developing severe disease [13]. Moreover, among adolescents, pregnancy and smoking (even passive smoking) are additional factors for severe disease presentation. Moreover, genetic polymorphisms of angiotensin converting enzyme 2 (ACE2) gene have been associated with Multisystem Inflammatory Response Syndrome in Childhood (MIS-C) presentation [13]. Finally, patients with blood group A have been reported to have a 45% higher risk of Covid-19 infection, whereas those with blood group O have the lowest risk [15] (Table 2).

1c. Severe conditions due to COVID-19 in children

Children infected with COVID-19 may rarely face certain critical conditions like multisystem inflammatory response syndrome (MIS-C) and the pediatric acute respiratory distress syndrome (P-ARDS), pericarditis, myocarditis and long COVID syndrome. The mortality rate of pediatric patients with P-ARDS has been reported to be very low, in contrast to that of adults with ARDS, which is very high (75%) [16].

Multisystem inflammatory response syndrome in COVID-19 infection (MIS-C)

The multisystem inflammatory response syndrome is an entirely new entity, affecting children and adolescents

recently infected with COVID -19. The clinical manifestations of MIS-C include prolonged fever, hypotension, multiorgan involvement (at least two organs), increased levels of inflammatory markers, D-dimmers and ferritin. The differential diagnosis of MIS-C includes Kawasaki disease, toxic shock syndrome and secondary macrophage activation syndrome [17].

The pathophysiology of MIS-C can be explained by the binding of the coronavirus glycoprotein S to the T- lymphocyte receptors, which results in the creation of a new complex, called T-cell receptor (TCR). This process renders SARS-CoV-2 to act as a superantigen, which stimulates the activation of a severe inflammatory reaction with the release of numerous proinflammatory and anti-inflammatory cytokines [18].

Kawasaki disease, an angiopathy also occurring in childhood, has many similarities with MIS-C. However, it affects younger children aged 6 months–7 years, while MIS-C seems to affect older children and adolescents aged 7–20 years. Among other differences between MIS-C and Kawasaki disease, are the type and the level of inflammatory cytokines' elevation. In particular, MIS-C presents with markedly increased TNF-a and IL-10, while Kawasaki syndrome is characterized by mild elevation of pro-inflammatory cytokines (IL-1, IL-2, and IL-6 but not IL-10). TNF-a seems to play a crucial role in the etiopathogenesis both of MIS-C and Kawasaki disease [17].

1e. Myocarditis and pericarditis associated with COVID-19 infection

Among the cells that SARS-CoV-2 is specifically attached to, are the cardiac myocytes. During the early phase of the disease (viremia), acute pericarditis, myocarditis, or cardiomyopathy related to sepsis may occur. During myocarditis, elevated levels of cardiac enzymes (troponin, NT-pro-BNP) as well as CRP and ESR levels are observed, accompanied by impaired ECG, 2D Echo Doppler and cardiac MRI. Delayed cardiac presentations include multisystem inflammatory syndrome in children and adolescents, coronary artery dilation or aneurysms, and late myocarditis, which may occur in the weeks following COVID-19 acute infection. During delayed presentations, PCR testing for SARS-CoV-2 is negative. Thus, these reactions seem to be due to a hyperinflammatory response following the viral infection. However, the long-term cardiac consequences COVID-19 are unknown. [19].

1f. Long term sequelae of COVID-19 in childhood

The range of long-term clinical conditions following COVID-19 in adults is well recognized. However, due to the paucity of long-term trials in childhood, the epidemiology and risk factors of long COVID-19 (or post-COVID-19 syndrome) in children are less understood. Thus, recent studies have shown that children with mild or asymptomatic SARS-CoV-2 infection may develop long-term symptoms, that include cough, fatigue, and lethargy. Additionally, it was observed that the epidemiology of common childhood respiratory viruses, such as respiratory syncytial virus (RSV) changed during the pandemic, while a type of hepatitis of unknown cause emerged in children with SARS-CoV-2 infection, possibly attributed to adenovirus type 41 [20].

These findings support the necessity of immunization programs for SARS-CoV-2 in children, and also infection surveillance on the epidemiology of other pediatric viral infections, such as adenovirus type 41 and RSV, in order to develop and administer relevant effective vaccines. Childhood immunization programs are being implemented globally to prevent the aforementioned direct and indirect medical consequences of COVID-19 including severe complications (e.g., MIS-C) and the long-COVID syndrome, as well as the indirect impacts of prolonged community and school closures on education, social and behavioral development, and mental health of children and adolescents. [21].

1g. Why children do not experience severe respiratory disease from COVID-19

Evidence suggests that children and adolescents are more likely to present with mild symptoms from COVID-19 infection and minimal involvement of the respiratory system. Different theories have been developed based on children's unique characteristics, such as the presence of a large amount of immature T lymphocytes and the expression of few ACE2 receptors. On the contrary, adults with severe Covid-19 infection present with severe immune derangement, characterized by lymphopenia and extreme production of pro-inflammatory cytokines (cytokine storm), leading to a severe immune reaction in the second phase of the disease [14].

Covid-19 and diabetes mellitus in children and adolechents

Diabetes mellitus and obesity, which usually accompanies type 2 diabetes, constitute two serious risk factors for the development of severe COVID-19 infection, especially in adults. It has been observed that COVID-19 infection has an impact on the frequency and the severity of both newly diagnosed and existing diabetes. Specifically, COVID-19 infection has been associated with:

A. Controversial effect on the frequency of newly diagnosed T1D in children and adolescents during the pandemic [22–24].

B. Notable increase in the frequency as well as the severity of diabetic ketoacidosis (DKA) during COVID-19 infection both at the time of T1D diagnosis, but also in the course of the disease [25].

2a. The prevalence of newly-diagnosed T1D during the COVID-19 pandemic

Most studies concerning the incidence of newly diagnosed T1D during the ongoing pandemic have conflicting results. Some studies report increased incidence [22], while others decreased [26] or unchanged incidence before and during the pandemic [23].

In a multicenter study from the United Kingdom including 30 children aged between 23 months and 16.8 years from March till June of 2020, a significant increase in the number of new cases of T1D and incidents of diabetic ketoacidosis (DKA) in comparison with the previous 5 years was observed [22]. Specifically, 70% of patients presented with DKA, of whom more than 50% had severe DKA. The prevalence of DKA in COVID-19 positive patients was higher compared to COVID-19 negative ones (80% vs 68%, respectively). Among the COVID-19 positive patients, three out of five encountered severe DKA with persistent hypokalemia, while one patient with severe hypokalemia presented with cardiac arrest, which was managed successfully in ICU [22].

A study of children with T1D registered to the Finish Diabetes Registry demonstrated that the incidence of newly diagnosed T1D increased from 38.7/100000 per year in 2016–2019 to 56.0/100 000 per year in 2020 with an IRR of 1.45 (95% CI 1.13–1.86) [26]. Nevertheless, none of the children who participated in the study tested positive for SARS-CoV-2 antibodies, hence this increase could not be attributed to the virus directly [26].

In a most recent study by Barett et al in the United States the diagnosis of new cases of diabetes in children younger than 18 years was 166% more likely to occur within 30 days post COVID-19 infection compared to those without COVID-19 during the pandemic [27]. It was also 116% more likely to occur in patients with COVID-19 compared to patients with other infections of the respiratory tract. The authors have attributed this increase to the effect of COVID-19 on the pancreatic b-cells. The limitations of this study included the low specificity in the definition of diabetes as it was based on the ICDM-10-CM code inserted in the registry, the lack of diagnosis confirmation for some patients classified as COVID positive and the non-examination of covariates, such as race/ethnicity, obesity and prediabetes status, that may have affected the association between COVID-19 and diabetes [27].

In another recent study by Shulman et al. [28] from data from the Canadian Diabetes Registry which included 2,700,178 children and adolescents aged 1–17 years, during the years 2017–2021, it was found that overall, during the pandemic, there was no difference in observed vs expected relative rates (RRs) of new diabetes presentations (RR, 1.09 [95% CI, 0.91–1.30]). However, RRs of new diabetes presentations decreased in the first 3 months of the pandemic (15–32% lower from March to May 2020), with a subsequent increase to higher-than-expected rates (33–50% higher between February to July 2021). The results of this study are very important as they come from one of the countries with the highest incidence of T1D and it includes epidemiological data on a large childhood population of a diabetes Registry. Nevertheless, these results should be confirmed by other large studies. Moreover, Tittel et al. reported no elevation in the frequency of T1D during the pandemic [23]. This study included data from 217 Pediatric Centers in Germany, from March 2020 till May 2020. The results revealed that the prevalence of newly diagnosed T1D during the first wave of the Pandemic in patients <18 years was 23.4/100.000 patient years, which did not differ significantly from the predicted incidence (22.1/100.000 patient years). Nevertheless, an increase in the incidence of T1D was found in boys (28.1 vs 23.1/100.00 patient years). The unchanged incidence of newly diagnosed T1D during the first wave of the pandemic and lockdown was attributed to the reduced incidence of most infections, which are important trigger factors for the manifestation of T1D [23]. Similarly, studies from Kuwait [29] and Canada [30] have found no increase in the prevalence of T1D new cases during the pandemic, compared to the previous years.

Finally, certain studies report a decreased frequency of COVID-19 infection in children with T1D. In particular, studies from China and Italy do not report cases of COVID-19 infection in patients with T1D [31]. The researchers attribute these results to [31]: 1) the younger age and the low prevalence of patients with T1D, 2) the increased protection measures against COVID-19 (quarantine) 3) and finally to the increased expression of CD8 + lymphocytes in T1D, which exerts protective effects against infections. CD8 + lymphocyte apoptosis is highly elevated in COVID-19 infection in adults, which leads to lymphopenia, a phenomenon that does not occur in pediatric patients. Nevertheless, pediatric patients with T1D are also infected by Sars-COV2 and some of them may need hospitalization, especially those with poor diabetic control [32].

2b) Frequency and severity of DKA during COVID-19 infection in children

Despite the questionable effect on the frequency of newly diagnosed T1D in children and adolescents of the COVID-19 pandemic, most studies concur that the pandemic has contributed to the increased frequency and severity of DKA during T1D diagnosis. This is confirmed by the study of Basatemur E et al from the United Kingdom [25]. The authors reported that 5 years before the pandemic a seasonal variation in the incidence of T1D was observed with an increase during winter and fall months and a reduction during summer and spring. A great reduction of T1D incidence was observed during the first wave of the pandemic. Regarding the incidence of DKA at diabetes diagnosis, the monthly distribution of DKA cases during the prior 5 years did not reveal any seasonal differences. Yet during the first wave of the pandemic, the frequency of DKA was increased [25].

Moreover, other studies from different countries have reported increased frequency of DKA in children with T1D during the pandemic [26, 27, 29, 30, 33]. Salmi et al. and Abdulrazaqq et al. have also reported an increased number of pediatric patients with DKA who required admission to the pediatric intensive care unit during the pandemic [26, 29], whereas Barret et al., Ho et al., and McGlaken et al. have also found an increased severity of DKA [27, 30, 33]. A meta-analysis of 20 studies showed that the risk of DKA and severe DKA was 35% and 76% higher in the COVID-19 era group compared to the prior to COVID-19 era group, respectively. Additionally, the risk of DKA in the newly diagnosed COVID-19 era group was higher (44%), compared to the prior to COVID-19 era group [34]. Two studies reported that the risk of DKA among T1D patients with established T1D was not significantly different during the pandemic, however it was noted that healthcare systems should take all necessary measures to prepare for an increase of DKA cases [34].

2c) Causes of increased frequency of DKA during newly diagnosed or former T1D

The increase in the frequency and severity of DKA in patients with T1D during the pandemic has been attributed to various factors such as the delay in diagnosis due to avoidance of hospital visits or due to the overload of Health Care systems [35], and also to the diabetogenic action of SarsCov2 virus [22] (Table 3). In more detail Salmi et al have reported that while ED visits were reduced by 45%, the diagnosis of DKA was delayed due to social distancing measures, the prioritization of COVID-19 infection control from the public health authorities and the parental fear of

Table 3 Causes of increased frequency of DKA for patients with newly diagnosed or preexisting T1D:

A. Delay in the diagnosis of DKA in patients withs newly diagnosed T1D due to: [43]

• Parental avoidance of hospital visits due to the fear of getting COVID-19 infection, restriction of transportation during lockdown periods etc.

• Delayed medical diagnosis because of:

    ■ Exclusive use of numerous hospitals for COVID-19 patients

    ■ Overlapping of DKA and COVID-19 infection symptoms

• COVID-19 infection increases the risk for DKA due to an increase in insulin resistance

B. Delay in the diagnosis of DKA in patients with preexisting T1D:

• Irregular follow-up by the Pediatric Endocrinologist → metabolic dysregulation

• Difficulties in acquiring insulin and diabetic expendable equipment (e.g blood glucose Test Strips and sensors, pump expendables)→ metabolic dysregulation

• Lifestyle alterations due to quarantine (decreased exercise, unhealthy diet)

• Online school courses (increased screen time)

contracting COVID-19. McGlacken et al have highlighted that apart from the fear of COVID-19, other factors such as the limitations of remote patient consultations, the lack of appreciation by parents of the severity of the disease and the difficulties in accessing healthcare services have also contributed to the increased frequency and severity of DKA during the pandemic. The authors also stated that children from families with T1D had less severe DKA and reduced hospitalizations [30].

Similarly, Abdulrazaqq et al. have reported that a family history of diabetes was associated with lower risk of presentation with DKA and admission to the PICU [29]. Ho et al. emphasize on the negative effect of medical staff redeployment and increased workload during the pandemic as well as the limitations of virtual clinics as causes for the increased frequency of DKA [30].

2d) The impact of lockdowns on diabetic control

Most of the studies from Europe and the USA agree that the quarantine had a beneficial effect on the diabetic control of children and adolescents with T1D [36–38]. According to these studies, the continuous glucose monitoring (CGM) devices yield better results in children and adults with T1D, while worse glucose levels were reported in adolescents. Furthermore, an improvement of metabolic control was reported in poorly controlled pediatric patients. Namely, the factors which contributed to this improvement of diabetic control were older age, stress, increased exercise, the use of CGM devices, the use of telemedicine and enhanced

parental supervision of pediatric patients during the quarantine [36–38].

On the other hand, a study from Malaysia reported a deterioration in diabetic control due to the lockdown measures [39]. The study included 93 children and adolescents <18 years with T1D and 30 with T2D. Although an improvement in the metabolic control in children with T1D due to increased parental monitoring was reported, a deterioration of glycemic control during the quarantine was shown for male patients, adolescents and patients with T2D. This was associated with the reduced number of meals, the elimination of breakfast, reduced exercise, increased screen time, sleep deprivation, weight gain in patients with T1D, and weight reduction in patients with T2D, possibly due to the deterioration of their glycemic control. In conclusion, this study overall reported that the quarantine had a negative impact on glycemic control and the lifestyle of male patients, adolescents and patients with T2D [39].

Types of diabetes during covid-19 infection

COVID -19 infection has been associated with the development of certain types of DM (Table 4): a) triggering an acute newly-diagnosed DM in children, adolescents, and adults (which has also been reported with SARS-CoV-1 and MERS) [40] and is characterized by the lack of pancreatic autoimmunity. Furthermore, COVID-19 infection may b) accelerate the manifestation of newly diagnosed T1D or T2D [41], or c) provoke severe metabolic dysregulation and life-threatening DKA in preexisting or newly diagnosed T1D [42]. Finally, it is assumed that SARS-CoV-2 may d) induce pancreatic autoimmunity in patients, with the possibility of T1D manifestation even years later [43].

Covid-19 infection and diabetes pathogenesis

Diabetes mellitus type 1 belongs to the family of autoimmune diseases, occurring in people with genetic predisposition. Pancreatic autoimmunity may be triggered by various environmental factors, such as viral infections,

Table 4 Types of diabetes after COVID-19 infection

A. Possible triggering of acute DM

B. Acceleration of newly-diagnosed diabetes manifestation (T1D or T2D)- development of severe DKA

C. In children with known T1D: severe metabolic derangement and DKA

D. COVID -19 infection possibly induces pancreatic autoimmunity in previously healthy children

reduced sun light exposure, resulting to vitamin D insufficiency, as well as severe acute or chronic stress [44]. Factors including the enteric microbiota, early exposure to cow's milk, early introduction of solid foods and cereals and increased birth weight have been increasingly recognized to play an important role in the development of pancreatic autoimmunity [45, 46]. On the contrary, exclusive breast feeding has been reported to have a protective effect against T1D development [45].

COVID-19 infection triggering acute DM

One type of T1D associated with the presence of viral infections is the acute diabetes type 1β-non autoimmune (fulminant) (90%). It is most commonly encountered among adults and it seems to be caused by direct lytic action of the virus on the pancreatic b-cells [47].

Most commonly, this type of diabetes is preceded by upper respiratory tract or gastrointestinal infections due to mumps virus, HHV6, HSV, Coxsackie B3-B4, hepatitis A, Influenza B, Parainluenza and recently SARS-CoV-2 etc. [48, 49]. Features of this type of diabetes include the presence of diabetic ketoacidosis, the short duration of symptoms (approximately 7 days), the absence of pancreatic autoantibodies, very low levels of endogenous production of insulin (C-peptide), increased levels of pancreatic enzymes and HbA1c < 8.5% at diagnosis [43].

Possible pathogenetic mechanism

SARS-CoV-2 infects and replicates in cells of the human endocrine and exocrine pancreas [50]. This has been confirmed by studies of autopsy samples, where the virus was found in β-cells [51]. The development of acute DM during COVID-19 infection can be explained by previous studies on SARS-CoV-1 virus, which has many similarities with SARS-CoV-2, published in the last decade [40]. The Angiotensin-converting enzyme 2 (ACE2) receptor is widely expressed in pancreatic β-cells and binds to SARS-CoV-1 and SARS-CoV-2 viruses. It was assumed that SARS-CoV-1 enters the pancreatic β-cells through the binding with the ACE2 receptor, which in turn results in cellular lysis. Lysis is facilitated through a) direct multiplication of the virus or b) circulatory antigens of the virus. The outcome is the development of transient diabetes. Studies in patients presenting with SARS-CoV-1 infection, have revealed an acute destruction of β- cells, without the presence of anti-pancreatic autoantibodies (T1D type 1B). The same mechanism may also underlie the action of SARS-CoV-2. Furthermore, pro-inflammatory cytokines produced during the infection, increase the expression of ACE2 in β-cells, and as a consequence enhance the susceptibility to COVID-19 infection [43, 52].

Moreover, Kazakou et al. in a recent review have reported that the SARS-CoV-2 virus may trigger the presentation of newly diagnosed diabetes mellitus, via a direct effect on pancreatic beta-cells [53]. In more detail, COVID-19 can have a direct cytolytic effect on β-cells, which in turn results in reduced insulin production and subsequent development of diabetes. Additionally, the virus results in the development of an immune response, with the release of chemokines and cytokines that affect pancreatic β-cells and impair their ability to sense glucose concentrations and release insulin. The cytokines produced may further affect the ability of liver, muscles, and other peripheral organs to uptake glucose [54]. This effect is mediated via the presence of ACE2 on the surface of β-cells, where the virus binds, which in turn results in inflammatory cytokine release, β-cell apoptosis, and decreased insulin secretion [55].

Additionally, ACE2 plays a crucial role in β- cell function and glucose homeostasis, according to studies in mice. A high fat diet may reduce the number of ACE2 receptors, while ACE2 deletion in diabetic mice promotes hyperglycemia, increases oxidative stress of β-cells, and reduces insulin secretion [56]. The angiotensin-converting enzyme 2/angiotensin (1–7)/Mas axis protects the function of pancreatic β-cells by improving the function of islet microvascular endothelial cells [57]. ACE2 deficiency reduces β-cell mass and impairs β-cell proliferation in obese C57BL/6 mice [58]. The above explain why the binding of SARS-CoV-2 on ACE2 receptors affects β-cell function and glucose homeostasis.

Acceleration of preexisting pancreatic autoimmunity

It is believed that the exposure to SARS-CoV-2 accelerates the development of ongoing T1D or T2D, through the release of cytokines and the activation of CD8 + T lymphocytes in people with a genetic predisposition, which leads to quicker destruction of β-cells (insulitis) and to earlier T1D or T2D presentation [22].

SARS-CoV-2 as a superantigen

The development of T1D with severe DKA, possibly occurs due to the action of SARS-CoV-2 as a superantigen [18]. Superantigens are produced during infection from bacteria (e.g., streptococcus, staphylococcus) or viruses (e.g., EBV, CMV, HIV). Superantigens induce the non-specific activation of T lymphocytes and the secretion of cytokines and interferon γ, which intensifies the secretion of cytokines. In this way, the superantigens cause a surge of proinflammatory cytokines, which lead to the development of multisystem inflammatory syndrome (MIS-C) [18]. MIS-C manifestation in patients with T1D occurs rarely [59].

COVID-19 infection and the pathogenesis of pancreatic autoimmunity

COVID-19 infection has been implicated in the development of pancreatic autoimmunity and subsequently T1D years after the infection.

The following mechanisms can theoretically explain the development of pancreatic autoimmunity [43]:

A. **Molecular mimicry**

Viruses carry epitopes which are similar to the β-cell epitopes. Presentation of the viral epitopes by antigen presenting cells activate autoreactive T cells that bind to both self and non-self antigens and induce β-cell destruction [60].

B. **Bystander activation**

Viral infections, by evoking β-cell damage, promote the release of self-antigens, which are then presented via specific antigen presenting cells (APCs) to the CD4 + T lymphocytes in the local lymph nodes, triggering the production of pro-inflammatory cytokines, and causing not only the destruction of the affected by the virus pancreatic β-cells, but also of the adjacent healthy α and δ cells of the islets. The destruction of β-cells leads to inadequate transformation of pro-insulin to insulin, thus reduced insulin production [61]. This hypothesis can explain the beginning of the autoimmune process.

C. **Chronic destruction of β-cells**

Some viruses, such as CMV and possibly SarsCOV-2 [62] may cause a state of chronic inflammation (as it was revealed by studies in organ donors). The MHC-1 molecules are proteins existing on the cell surface and contribute to their identification from the immune system, especially from the T-lymphocytes and the natural killer cells (NK). During inflammation both type α and β-interferons are released in the circulation and activate the immune system. Chronic inflammation leads to chronic overexpression of MHC-1 and to continuous presentation of the destroyed β cells to the immune system, leading to pancreatic autoimmunity [62].

Clinical presentation and course of disease in patients with newly diagnosed DM during Covid-19 infection

Acute DM in adults during COVID-19 infection

There are a few case reports on acute DM during COVID-19 infection in the literature. Kuchay MS et al report on

three cases of adult men (ages 30, 34, and 60), who presented with acute DM and DKA during COVID-19 infection [63]. All three patients were overweight, without other underlying conditions. One presented with bacterial pneumonia and severe DKA, while the other two had DKA of moderate severity.

At DM diagnosis, the patients had elevated levels of HbA1c: 9.6–12.6%, IL-6, ferritin and d-dimmers. The PCR SARS-CoV-2 was positive, while the anti-pancreatic autoantibodies (anti GAD) were negative. The patients were admitted to the Intensive Care Unit (ICU) and treated according to the DKA protocol, with intravenous fluids and insulin, while the patient with pneumonia received further antiviral factors (Remdesivir), empirical antibiotic treatment and corticosteroids. After DKA management, the patients were treated with sc basal/bolus insulin regime (4 injections/24 h), received diabetes education and were discharged in the third week after admission. Six weeks after the onset of symptoms, the total daily insulin dose was gradually reduced and patients were commenced on oral antidiabetic medication (metformin and sitagliptin), with further gradual reduction of insulin daily requirements. The eighth week, insulin treatment was discontinued and patients remained only on oral antidiabetic agents. Approximately three months later, they maintained optimal diabetic control (HbA1c: 6.2–7.4%) [63].

Furthermore, a study from Germany reported the case of a 19-year old male who developed insulin dependent DM and DKA without the presence of antipancreatic antibodies 5–7 weeks after symptomatic COVID-19 infection [47]. In conclusion, the three patients contracted COVID-19 infection in the stage of prediabetes or asymptomatic T2D, and they presented with symptomatic T2D and DKA via the acute cytotoxic action of the virus resulting in acute insulin insufficiency. After many weeks/ months there was a gradual reduction in insulin requirements, and continued on oral antidiabetic medication as T2D patients. However, the fourth patient developed acute T1D after COVID-19 infection, due to the acute destruction of β-cells and was managed with basal/bolus sc insulin regime.

Children and adolescents with COVID-19 and newly-diagnosed T1D

Current literature describes four cases of newly diagnosed T1D in children and adolescents during COVID-19 infection [59, 64–66]. The patients were three males and one female, with ages ranging between 8 months and 16 years (Table 5). All patients reported a history of classic diabetes symptoms for 1–2 weeks before the diagnosis of T1D. They presented to the hospital with fever, dehydration, tachypnea and respiratory distress. All had elevated glycose levels

Table 5 Clinical presentation of T1D during COVID-19 infection in childhood

Authors	Clinical presentation	Laboratory testing	Imaging	Treatment	Follow-up
Benyakhlef et al. [64]	3-year-old male, polyuria & polydipsia	Glu: 300 mg/dl, pH:7.25, **K:2.7** mEq/lt, PCT:3.4 ng/L, **HbA1c:10%, anti-GAD: 60 U/ml (<5)**	**Chest CT: Bilateral ground glass opacity and infiltrations**	IV insulin→ sc, IV fluids + KCL, high flow NC O$_2$	Basal/bolus insulin regimen
Robazadeh et al. [65]	16-year-old male, polyuria, polydipsia, weight loss, T: 38.2 °C, SaO$_2$;94%,	Glu:512 mg/dl, pH:6.9, HCO3: 8 mEq/lt, CRP:44 g/Lt, **HbA1c: 8.5%, c-peptide: 0.25 ng/ml**	Chest CT: unremarkable	IV insulin→ sc, IV fluids + KCL, hydroxychloroquine +Lopinavir /ritonavir	Basal/bolus insulin regimen
Soliman et al. [66]	8-month-old male, lethargy, fever, tachypnea, dehydration	Glu: 571 mg/dl, pH: 7.08, HCO$_3$: 7 mEq/ Lt, K: 5.6mEq/lt, **HbA1c: 12.9%,** CRP:4.2 g/L, **anti-GAD:34 U/lt(<5), c-peptide: 0.43 ng/ml**	Chest X-ray: unremarkable	IV insulin + IV fluids	Basal/bolus insulin regimen
Naguib et al. [59]	8-year-old female, polyuria, polydipsia, conjunctivitis, cough, MIS-C	Glu: 429 mg/dl, pH:7.3, HCO$_3$:14 mEq/ Lt, K:3.4 mEq/lt, CRP: 2.41 g/lt. **Fibrinogen: 8.16 g/L, D-dimers: 955 ng/ml, HbA1c:12%, SARSCoV2 IgG:9.7 (N <0.7)**	**Chest X-ray: pleural effusions**	Sc insulin, total daily dose: 1.4 IU/kg/day, methylprednisolone: 1mg/kg BID, IVIG: 2g/kg, infliximab: 10 mg/kg	Basal/bolus insulin regimen (dose 1.1 U/kg/day), HbA1c (in 1 month):7.8%

In bold are the abnormal laboratory testing results and imaging findings

(300–571 mg/dl), whereas two patients had severe and two mild DKA. One patient also presented with severe hypokalemia (K: 2.7 mEq/lt) which was treated with high doses of KCL. HbA1c levels were increased in all children, C-peptide was low, and all patients had elevated levels of anti-pancreatic autoantibodies. Two out of 3 patients presented with severe respiratory disease, and one of them also developed MIS-C. All children were treated according to the DKA protocol, while COVID-19 infection and its complications were treated appropriately (Table 5). The patient with MIS-C required high doses of sc insulin to achieve diabetes control (1.4 IU/kg/24 h) [59]. All patients were discharged from the hospital in a good clinical condition on a multiple daily injection insulin regime and their clinical course remained stable (Table 5).

The development of MIS-C in patients with T1D and DKA during COVID-19 infection is a rare complication and could be explained as follows: the increased levels of proinflammatory cytokines during severe DKA [67] may further be aggravated by the presence of COVID-19 infection, which also stimulates the release of numerous proinflammatory and anti- inflammatory cytokines, leading to the development of MIS-C [18].

The association of DKA with MIS-C implies that children may be vulnerable to the post-COVID-19 immunological and inflammatory side-effects [68].

Complications after Covid-19 infection and T1d in children and adolechents

Pediatric patients with newly diagnosed T1D during COVID-19 infection or with pre-existing diabetes may face the following complications:

a. Increased frequency of severe DKA
b. Increased risk of severe and refractory hypokalemia during DKA
c. Increased risk of MIS-C during DKA (rarely encountered) [34].

The possible pathophysiological mechanism for the development of these complications are described as follows:

DKA pathogenesis during COVID-19 infection [34]

Impaired glycemic control and increased susceptibility to infections

Hyperglycemia alters normal immune response, resulting in the production of increased levels of proinflammatory cytokines, which are increased in parallel with the degree of

severity of DKA [67]. This increase in turn leads to proinflammatory and pre-thrombotic state. Thus, there is elevated secretion of TNF-a, IL-6 and D-dimmers, increasing the risk of bacterial and viral infections (SARS-CoV-2) [42]. On the other hand, the glycosylation of ACE2 receptors (necessary for the entrance of the virus in the cells) is increased during prolonged hyperglycemia and subsequently enhances the vulnerability to SARS-CoV-2 infection. Therefore, the importance of optimal glycemic regulation is vital for the better management of COVID-19 infection [69].

Mechanisms of insulin resistance during COVID-19 infection

COVID-19 infection results in severe hyperglycemia due to an increase in insulin resistance. This results in massive secretion of proinflammatory cytokines (TNF-a, IL-1b, Il-6, MCP-1, C3), which are related to insulin resistance and subsequently leads to the development of DKA in patients with preexisting or newly diagnosed DM [70].

Furthermore, the inflammatory response which is triggered by the virus, induces the secretion of compensatory hormones (cortisol, adrenaline), which further aggravate hyperglycemia and activate the renin angiotensin-aldosterone-system (RAAS); this leads to β-cell destruction either by direct lytic action of virus to the cells or through the production of proinflammatory cytokines which is stimulated by the virus. In this way the manifestation of diabetes is accelerated during COVID-19 infection [71].

Thus, Boddu et al. [43] report that there is a two-way correlation between COVID-19 infection and diabetes. On one hand, the infection may cause acute β-cell destruction exacerbating the manifestations of ongoing T1D or T2D or resulting in the presentation of acute diabetes. COVID-19 infection also increases insulin resistance and leads to metabolic dysregulation and DKA in patients with pre-existing diabetes. Additionally, COVID-19 can result in hyperglycemia in two possible ways. Firstly, the use of steroids or antiviral agents for the management of COVID-19 infection may occasionally cause transient hyperglycemia and insulin resistance [72] and secondly, the increase in the body mass index due to the pandemic lockdown measures [27]. On the other hand, in patients with diabetes and poor glycemic control, the susceptibility to COVID-19 infection is increased due to glycosylation of the ACE2 receptors, which are necessary for the viral entrance into the cells, resulting in reduced immune response of these patients [73]. Taking into account the global rise in diabetes prevalence, it has been reported that the two pandemics (COVID -19 and diabetes) interact with each other [74]. This situation highlights the importance of the optimal diabetic control for better outcome of the COVID-19 infection.

Mechanisms of severe hypokalemia during DKA in COVID-19 infection

Another complication encountered in pediatric patients with newly diagnosed T1D and DKA during COVID-19 infection is refractory and severe hypokalemia [75]. A case of a child with COVID-19 infection and newly diagnosed T1D and DKA, who developed cardiac arrest due to severe hypokalemia successfully treated in the ICU, was reported [22].

Refractory hypokalemia in patients with COVID-19 infection and DKA can be explained by the following mechanism: COVID-19 infection is associated with low expression of ACE2 receptors, leading to reduced degradation of angiotensin II and increased aldosterone production, which is accompanied by potassium loss in the urine. Urine potassium loss worsens the hypokalemia, that usually follows DKA and is due to the movement of potassium cations during metabolic acidosis from the extracellular to the intracellular space due to insulin administration [76]. This, in association with potassium urine loss, could result in severe hypokalemia during COVID-19 infection and the need for high doses of potassium chloride for its management [74].

The severity of Covid-19 in children with T1d in comparison with healthy children and adults with T1d

Increased mortality was observed in adult patients with diabetes and COVID-19 infection. In Italy, 35.5% of patients who died from COVID-19 infection had DM, a three times higher rate than the general population [77]. Patients with DM were admitted to the ICU 4 times more frequently (22.2% vs 5.9%, $p = 0.009$) and presented with ARDS 2.3 times more frequently ($p = 0.002$). Moreover, they had increased severity of COVID-19 infection, multi-system impairment and increased mortality comparing with the general population [77].

Risk for hospitalization in children with T1D and COVID-19

On the contrary, children, adolescents and young people with T1D (<25 years) seem to have a different course of COVID-19 infection compared to healthy people of the same age [78].

A study from Italy that included 15.500 children with T1D reported that only 11 were infected with SARS-CoV- 2 and none of them needed hospitalization [79]. According to two more studies from the USA and Spain including 755 and 734 children with T1D respectively, only a few children had COVID-19 infection (2 and 3, respectively) and one had severe disease requiring hospitalization [80]. Studies from Italy and China [79, 80] with increased COVID-19 infection incidence report on low infection rates in children with T1D. This has been attributed to: 1. The younger age of T1D patients, 2. The low prevalence of children and adolescents with T1D, 3. Increased measures for Covid-19 prevention in different countries (lockdown etc), 4. Increased expression of CD8 + T lymphocytes in T1D patients, which exerts a protective role during COVID-19 infection [79].

The frequency and severity of DKA in children with T1D and COVID-19 infection was reported in a study including 266 children <19 years old with known T1D from 46 Diabetes Centers in the USA [81]. From the total study population, only 61 children (22,9%) needed hospitalization. DKA was the most severe complication and was reported in 72% of hospitalized children. Other severe complications, such as severe hypoglycemia [only in three patients (4.9%)], were rare. Severe respiratory distress occurred only in three patients (4.9%), of whom two were intubated, one patient developed MIS-C and ten patients were hospitalized for other reasons [81].

This study identified risk factors for hospitalization in children with T1D and COVID-19 such as belonging to an ethnic minority, poor diabetic control (HbA1c:11% vs 8,2%, $p = 001$), and less frequent use of diabetes technology (insulin pumps or continuous glucose monitoring devices (CGM) (pumps:26% vs 54%, $p = 0,001$, CGM devices: 39% vs 75% $p = 001$) [81]. Therefore, they concluded that children with T1D do not have increased risk for hospitalization due to COVID-19 infection and when infected, usually do not present with severe disease like adults. However, poor glycemic control was the major risk factor for hospitalization in pediatric patients with T1D during COVID-19 infection [81, 82].

Why children with T1D are less severely affected by COVID-19 compared to adults?

As it is reported by Tatti et al., children with T1D seem to be protected against COVID-19 infection in comparison with the adult population [83]. This can be explained by the strong Th1 immunity in young ages, which is mainly proinflammatory and mediated through T-lymphocytes via the secretion of IL-6 and interferon γ, the principle mechanism of action against viruses (e.g SARS-CoV-2) [84]. Th1 immunity is also related to the pathogenesis of autoimmunity (i.e.,T1D, Hashimoto thyroiditis, celiac disease etc) [85]. On the contrary, Th2 immunity which is common in older ages, is mediated through B-lymphocytes and the production of antibodies [86].

Hence, the milder form of COVID-19 infection in children with T1D is attributed to the higher prevalence of

Th1 against Th2 immunity. Furthermore, the over-expression of CD8 + lymphocytes in children encountered in T1D may also have a protective effect against COVID-19 infection [77].

Vaccination against COVID-19 in children with T1D

Vaccines have been developed to contribute to the fight against COVID-19 pandemic. To date two vaccines have received authorization for use in children, the Pfizer vaccine (from the age of 5 years) and Moderna mRNA vaccine (from 12 years) [87, 88]. The recommendations regarding vaccination of children against COVID-19 vary according to the country.

Although the duration and severity of clinical presentation of COVID-19 in children and adolescents is lower than in adults, there are rare severe complications, such as MIS-C, myo-or pericarditis and Long COVID syndrome [16–21]. Moreover, lockdown measures have negatively affected education and social development of children and adolescents [89]. Thus COVID-19 vaccination of those aged <18 years has been considered an additional measure for disease control [90].

The role of COVID-19 vaccine in patients with diabetes has been extensively reviewed and clinical data supports prioritization of adult patients with T1D or T2D for receiving the vaccine, as the infection has poor prognosis and is associated with more complications [91, 92].

Although children and adolescents with T1D do not present with severe clinical symptoms during COVID-19 in comparison with adult patients, they may present metabolic derangement and especially those poorly controlled, leading to DKA [21, 42], or very rarely MIS-C [59]. The side-effects of vaccination for pediatric populations are mild and more frequent after the second dose, without severe unfavorable outcomes [93]. Regarding the effect of COVID-19 vaccination in children and adolescents with T1D older than 12 years, it has been reported that it is safe, without significant effect on their glycemic control [94].

The various Pediatric Diabetes and Endocrine Societies have conflicting recommendations regarding COVID vaccination for children and adolescents. A study from the USA has recommended vaccination against COVID-19 in children to prevent the development of T1D associated with the disease [92]. The European Society for Pediatric Endocrinology (ESPE) does not recommend vaccination against COVID-19 in well controlled endocrine conditions, but only in those with poorly controlled T1D or those with severe obesity, who are at increased risk for severe disease [95].

The Israeli Pediatric Association has conducted a risk–benefit analysis regarding the vaccination of children and adolescents older than 5 years and concluded that vaccines are safe and effective and are recommended for all

children aged 5 to 11 years to protect them from COVID-19 and its complications and to reduce community transmissions [96]. Similarly, the American Diabetes Association (ADA) follows the CDC recommendation to vaccinate all children aged 5 years and older [97, 98]. Moreover, a multi-model aggregation study suggests that, expanding vaccination to children 5-11 years old would be directly beneficial to this age group and indirectly to the all-age U.S. population, including protection against more transmissible variants [99].

Thus, based on the current reports on the risks and benefits of vaccination against COVID-19 in the pediatric age-group and the benefit of the prevention of disease transmission, it is concluded that vaccination against COVID-19 in childhood is safe and effective and is recommended for all children and adolescents older than 5 years, especially those belonging to the high-risk groups for severe disease, such as those with poorly controlled T1D, obesity, or other comorbidities.

Conclusion

This review summarizes the current data regarding the association of COVID-19 infection with diabetes in childhood. It seems that children present with milder disease and shorter duration than adults, better prognosis and low mortality. Serious complications of COVID-19 infection in children include MIS-C, myo-or pericarditis and, less frequently, long COVID syndrome.

There are conflicting results in terms of the prevalence of newly diagnosed T1D in children during the pandemic. Nevertheless, all studies agree that there is an increase in the frequency and severity of DKA during T1D diagnosis. The types of diabetes associated with COVID-19 infection include acute newly diagnosed DM, the acceleration of development of T1D or T2D and the development of pancreatic autoimmunity. Children with T1D are less severely affected by COVID-19 than adults, while a deterioration of glycemic control in both adults and children with known DM has been observed.

Thus, the best way to prevent severe COVID-19 infection among adult patients with known T1D is to improve glycemic control. Moreover, due to the association of COVID-19 infection with diabetes presentation, clinicians should be alert for the identification of signs and symptoms of diabetes during or after COVID-19 infection to make the diagnosis promptly and prevent the development of DKA.

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Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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