



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



Contents available at [ScienceDirect](https://www.sciencedirect.com)

Diabetes Research
and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres



International
Diabetes
Federation



Review

Caring for children and adolescents with type 1 diabetes mellitus: Italian Society for Pediatric Endocrinology and Diabetology (ISPED) statements during COVID-19 pandemia



Giuseppe d'Annunzio ^{a,*}, Claudio Maffei ^b, Valentino Cherubini ^c, Ivana Rabbone ^d,
Andrea Scaramuzza ^e, Riccardo Schiaffini ^f, Nicola Minuto ^a, Gianluca Piccolo ^a,
Mohamad Maghnie ^{a,g}

^a Pediatric Clinic and Endocrinology, Regional Center for Pediatric Diabetes, IRCCS Istituto Giannina Gaslini, Genoa, Italy

^b Pediatric Diabetes and Metabolic Disorders Unit, University Hospital, Verona, Italy

^c Department of Women's and Children's Health, G. Salesi Hospital, Azienda Ospedaliero-Universitaria Ospedali Riuniti Ancona, Italy

^d Division of Pediatrics, Department of Health Sciences, University of Piemonte Orientale, Novara, Italy

^e Pediatric Unit, Ospedale Maggiore, ASST Cremona, Italy

^f Diabetes Unit, Bambino Gesù Children's Hospital, Rome, Italy

^g Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health Department of General and Specialist Pediatric Sciences, Pediatric Clinic, IRCCS Giannina Gaslini Institute, University of Genova, Genoa, Italy

ARTICLE INFO

Article history:

Received 28 May 2020

Received in revised form

22 July 2020

Accepted 11 August 2020

Available online 20 August 2020

Keywords:

Type 1 diabetes mellitus

COVID-19 pandemia

Clinical recommendations

Infectious disease

Pediatric age group

Clinical research

ABSTRACT

Aims: Our study aimed to review the impact of COVID-19 pandemia in children and adolescents with type 1 diabetes mellitus, to analyze the clinical characteristics of the infection and to propose clinical practice recommendations from the Italian Society for Pediatric Endocrinology and Diabetology (ISPED).

Methods: A literature search was carried out in the guideline databases, Medline and Embase and in Diabetes Societies websites until May 21st, 2020 for guidelines and recommendations on type 1 diabetes mellitus management during COVID-19 pandemic.

Results: COVID-19 infection in pediatric patients seems to be clinically less severe than in adults; children have so far accounted for 1–5% of diagnosed cases, with a median age of 6.7 years (1 day–15 years) and better prognosis. Clinical manifestations include mild, moderate, severe disease up to critical illness. There is currently no evidence suggesting a higher risk of COVID-19 infection in children with diabetes than unaffected peers. Besides general recommendations for pediatric patients, ISPED has proposed specific measures for patients with diabetes.

* Corresponding author at: Pediatric Clinic and Endocrinology, Regional Center for Pediatric Diabetes, IRCCS Istituto Giannina Gaslini, Genoa, Italy, Via Gaslini 5, 16147 Genia, Italy. Tel.: +3901056362366.

E-mail address: giuseppedannunzio@gaslini.org (G. d'Annunzio).

<https://doi.org/10.1016/j.diabres.2020.108372>

0168-8227/© 2020 Published by Elsevier B.V.

Conclusion: COVID-19 outbreak modified type 1 diabetes management, and telemedicine has been demonstrating to be an effective new tool for patients care. Moreover psychological aspects deserve attention and future researchs are mandatory.

© 2020 Published by Elsevier B.V.

Contents

1. Introduction	2
2. Methods	2
3. Results	2
3.1. COVID-19 in pediatric patients	2
3.2. Diabetes mellitus and infectious diseases	3
3.3. Quantifying COVID-19-related risks for patients with diabetes mellitus	3
3.4. Adaptation of standard-of-care treatment regimens	6
4. Patient education and psychological care	8
5. COVID-19 and pediatric diabetes: ISPED practical recommendations	8
6. Organizational strategy for future scenarios	8
7. Critical research priorities	8
8. Conclusions (Sharing experience)	8
Declaration of Competing Interest	9
Acknowledgement	9
Funding source	9
References	9

1. Introduction

In December 2019 a new RNA betacoronavirus infection emerged in Wuhan, China [1]. It has been recognized as causative factor of severe pneumonia and other systemic complications [1]. At the end of January 2020, the WHO named this betacoronavirus infection COVID-19 and defined it as a global epidemic communicable form of pneumonia. The disease spread rapidly worldwide and by March 11 the COVID-19 outbreak was classified as a pandemic disease [2]. Compared with other previous coronavirus epidemics [i.e Severe Acute Respiratory Syndrome (SARS) in 2003, and Middle East Respiratory Syndrome (MERS) in 2014], COVID-19 has spread more rapidly, probably because of increased globalization, inadequate risk assessment and other unknown environmental factors [3].

The most recognized form of COVID-19 transmission is through large respiratory droplets. The virus has been also found in tears, urine and stool of affected individuals [4]. The clinical features of the COVID-19 infection vary from being asymptomatic to fever, dry cough and fatigue up to acute respiratory distress syndrome with multiorgan involvement and death [5]. Other symptoms include sore throat, headache, abdominal pain, and diarrhea. Median age of infected individuals is in 50s, with a prevalence of male gender [4]. Infected adult patients who developed acute respiratory distress syndrome were usually affected by other comorbidities [5].

The aim of our study was to analyze available data about COVID-19 infections and type 1 diabetes mellitus, and to

formulate recommendations for children and adolescents with or who may develop type 1 diabetes mellitus in the time of Covid-19 infection.

2. Methods

A literature search was carried out in the guideline databases, Medline and Embase and in Diabetes Societies websites until May 21st, 2020 for guidelines and recommendations on type 1 diabetes mellitus management during COVID-19 pandemic. The search terms used were: COVID or COVID-19 or coronavirus or SARS-CoV2, and type 1 diabetes mellitus, and children, and adolescents, and recommendations. The searches were limited to papers published in English. A descriptive analysis was performed.

3. Results

3.1. COVID-19 in pediatric patients

COVID-19 infection in pediatric patients seems to be clinically less severe than in adults; children have so far accounted for 1–5% of diagnosed cases, with a median age of 6.7 years (1 day–15 years) and better prognosis [6–9]. The hypothesis that children are less susceptible to COVID-19 is intriguing, since newborn and infants can be infected, even if vertical transmission has not been certainly ruled out [10,11]; a lower risk has been recently ascribed to an age-dependent expression of Angiotensin-Converting Enzyme 2 (ACE2). ACE2 in nasal epithelium is the first point of contact for SARS-CoV-2

and the human body [12]. Incubation period is about 1–14 days, up to 24 days. Children affected by COVID-19 infection are generally asymptomatic increasing the risk of prolonged spreading of the outbreak. In fact, in more than 90% of affected children, the infection is clinically silent or is characterized by mild to moderate disease, while, in 5.2% of cases, severe form and in 0.6% critical illness have been described [7].

Otherwise, different clinical presentations have been described, including low fever, dry cough, wheezing, fatigue, nasal congestion, abdominal pain, nausea, vomiting, and diarrhea. Clinical manifestations include mild, moderate, severe disease up to critical illness, including severe pneumonia, septic shock, refractory metabolic acidosis, coagulation dysfunction [13]. No chest abnormalities have been reported in 20% of affected children; in the remaining cases chest computed tomography imaging have revealed unilateral or bilateral sub pleural ground glass opacities, and consolidation with surrounding halo sign, without pleural effusion [14]. COVID-19 pneumonia can be superimposed with other types of pathogens, particularly in children with other comorbidities, therefore imaging data might be more complex. Household contact with affected family members seems the main route of transmission. Moreover, the more active innate immune response, the healthier respiratory tract and the fewer comorbidities as compared to adults, as well as the different distribution, maturation, and functioning of viral receptors might partially explain the relative resistance to COVID-19 infection [15]. Recently the Coronavirus Infection in Pediatric Emergency Departments (CONFIDENCE) study has been published. It involved a cohort of 100 Italian children younger than 18 years of age with confirmed Covid-19 infection, who referred to pediatric emergency departments between March 3 and March 27. The peculiarity of this work lies in having identified, in addition to the common symptoms (44% of the patients presented with cough), also other more specific symptoms of early childhood, such as no feeding or feeding difficulties (23% of children). In this cohort 9 patients received respiratory support [16].

3.2. Diabetes mellitus and infectious diseases

Previous observations report an increased susceptibility to infections among patients with both type 1 and type 2 diabetes mellitus, responsible of increased morbidity and mortality [17–20]. Hyperglycemia may increase the virulence of different pathogens by enhancing bacterial replication and facilitating their attachment to epithelial cells favoring immune system dysfunction [21–23]. A study aimed to evaluate humoral factors in pediatric patients with type 1 diabetes showed lower IgG and C3 levels in poorly controlled disease as compared to patients with satisfactory degree of metabolic control [24].

Moreover, several viral infections have been considered as possible triggers of the autoimmune process leading to clinically overt type 1 diabetes mellitus, and infectious diseases may accelerate the clinical onset in at risk subjects [25–28].

Several case reports describe severe infections both in affected children and adults and underline the importance of considering infectious diseases prompt diagnosis, treat-

ment and, when available, prevention as goal for good management of the disease [29–32]. Similarly, diabetic ketoacidosis recovery may be delayed by concomitant infectious disease [33].

A US study in 77% type 1 and 23% type 2 diabetes adolescents reported that respiratory infections were the most common kind of infections, responsible for emergency care, hospitalization, increased economic impact, and health care cost [34].

American Diabetes Association Clinical Practice Recommendations consider vaccinations mandatory for patients, especially for seasonal influenza and pneumococcal infection [35].

Despite several evidence suggests the importance of vaccination in patients with diabetes mellitus, and the lack of association between vaccinations and autoimmunity [36], global coverage is still lower than expected [37–42].

As regards previous MERS and SARS outbreaks, to our knowledge no data are available regarding clinical course and sequelae in pediatric patients. On the other hand vaccination against H1N1 virus was not associated with increased risk of islet autoimmunity or type 1 diabetes, and in a group of Italian patients we did not report an increased risk of hospitalization due to H1N1 infection in pediatric patients with type 1 diabetes [43].

3.3. Quantifying COVID-19-related risks for patients with diabetes mellitus

Adult patients with diabetes are included in high risk group for COVID-19 infection with high mortality and morbidity rate. Diabetes mellitus and COVID-19 infection might share more links than expected. Both diseases represent a severe pandemics and are characterized by multiorgan involvement, even if with peculiar differences: chronic versus acute condition, communicable versus non communicable, both with unknown, at present, and known long-term complications. Even if common opinion associates diabetes with higher morbidity and mortality due to infections, it is still unknown if and how it represents a risk factor for prognosis of COVID-19. Diabetes mellitus is indeed one of the most frequent comorbidities observed in patients with COVID-19 infection. Some authors described that patients with severe disease, as compared with subjects with more mild infection, had diabetes as a common comorbidity [44].

On the other hand, since in patients with diabetes any infectious disease worsens the degree of metabolic control with a negative effect on the recovery, also COVID-19 infection may generate a vicious circle that would be detrimental for a better prognosis. It is also important to consider that COVID-19 receptors ACE2 are expressed on several organs and tissues, with a consequent risk of multiorgan failure other than lung involvement [45].

A recent study aimed to establish if diabetes is a risk factor influencing the outcome and prognosis of COVID-19 reported that adult patients without other comorbidities were at higher risk of severe pneumonia, showed higher tissue enzyme levels indicating multiorgan involvement, uncontrolled inflammatory response and hypercoagulable state together with dysregulation of metabolic control, even if insu-

Table 1 – Summary of reviewed papers looking at the impact of COVID-19 infections and diabetes mellitus.

Date, Title of paper, Authors	Study type	Aim of the study	Outcomes
January 30th, 2020 Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan China: a descriptive study. <i>Lancet</i> 2020;395(10223):507–513 [44]	Original article. Retrospective single centre study of 99 patients admitted from 1st to 20th January 2020, including adult cases of COVID-19 confirmed by RT-PCR.	To clarify the epidemiological and clinical characteristics of 2019-nCoV pneumonia.	Comorbidity is a worsening predicting factor: 51% had chronic medical disease of whom 24% had diabetes mellitus.
February 24th, 2020 Wu Z, McGoogan JM. Characteristics of and important lesson from the Coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72,314 cases from the Chinese center for disease control and prevention. <i>J Am Med Ass</i> 2020 Feb24. doi.org/https://doi.org//10.1001/jama.2020.2648 [50]	Opinion article, viewpoint. Among a total of 72.314 cases, the overall case-fatality rate (CFR) was 2.3%.	To summarize key findings from Chinese cases of COVID-19 epidemic.	Comorbidities including diabetes increase the risk of adverse outcome in COVID-19 infection. CFR was elevated among those with diabetes: 7.3%. No deaths occurred in the group aged 0–9 years.
March 10th, 2020 Gupta R, Ghosh A, Singh AK, Misra A. Clinical considerations for patients with diabetes in times of COVID-19 epidemic. <i>Diabetes Metab Syndr</i> 2020;14:211–12 [65]	Clinical considerations.	To increase the knowledge on SARS-CoV-2 infection's management in patients with diabetes.	Diabetic patients have an increased risk of infection with SARS-CoV-2. Comorbidities and older age worsen the prognosis.
March 28th, 2020 Fadini GP, Morieri ML, Longato E, Avogaro A. Prevalence and impact of diabetes among people infected with SARS-CoV-2. <i>JEI</i> 2020; https://doi.org/https://doi.org/10.1007/s-40618-020-01236- [49]	Letter to the Editor.	To report the results of a meta-analysis and of local data, showing the prevalence of diabetes among adults with COVID-19	Diabetes does not increase the risk of SARS-CoV-2 infection but can worsen the outcome of COVID-19. The rate ratio of diabetes among patients with adverse disease course was 2.26 in China and 1.75 at the University Hospital of Padua (Italy).

<p>March 31st, 2020</p> <p>Guo W, Li M, Dong Y, Zhou H, Zhang Z, Tian C, et al. Diabetes is a risk factor for the progression and prognosis of COVID-19. <i>Diabetes Metab Res Rev</i> 2020;e3319.</p>	<p>Research article.</p> <p>Retrospective study on 174 adult patients, admitted from 10th to 29th February 2020.</p>	<p>To define whether diabetes influences COVID-19 infection.</p>	<p>Diabetes is a risk factor for rapid progression and bad prognosis of COVID-19 pneumonia.</p>
<p>March 31st, 2020</p> <p>Muniyappa R, Gubbi S. Perspective: COVID-19 pandemic, coronaviruses, and diabetes mellitus. <i>Am J Physiol Endocrinol Metab</i> 2020 May 1; 318(5): E736–E741 [46]</p>	<p>Research article.</p> <p>Pathophysiology study.</p>	<p>To summarize clinical features and natural course of COVID-19, its pathophysiology and the potential mechanisms by which diabetes modulates the host-viral interaction and host immune responses.</p>	<p>Importance of identification of clinical and biochemical parameters using multiomics approaches, that predict severity of COVID-19 in patients with diabetes.</p>
<p>April 17th, 2020</p> <p>Garg SK, Rodbard D, Hirsch IB, Forlenza GP. Managing new-onset type 1 diabetes during the COVID-19 pandemic: Challenges and opportunities. <i>Diab Technol Therap</i> 2020;22(6):1–9. [66]</p>	<p>Original article</p>	<p>To define the role of telemedicine in type 1 diabetes management</p>	<p>Telemedicine in an effective approach for the management of new-onset type 1 diabetes particularly during COVID-19 pandemic</p>

lin requirement increased after infection [46]. Worsening of metabolic control affects severity of pneumonia, together with the coexistence of comorbidities. Therefore, diabetes should be considered as a risk factor for the inflammatory storm leading to rapid worsening of COVID-19 infection.

Potential mechanisms increasing the risk of COVID-19 among patients with diabetes are higher affinity cellular binding and efficient virus entry into the cells, decreased virus clearance, reduced T cell function, increased susceptibility to cytokine storm [47]. Increased expression of ACE2 has been observed in the lung, kidney, heart, pancreas in animal models of diabetes [48]. Moreover, higher levels of furin, a cellular protease facilitating virus entry, have been observed in patients with diabetes mellitus [49].

As for the impact of diabetes among adults COVID-19 infected Italian patients, it has been reported that the prevalence of pre-existing diabetes was 8.9%, and the ratio of diabetes in patients who died for COVID-19 infection as compared to general population was 1.75 [50]. The authors concluded that diabetes does not increase the risk of COVID-19 infection, but can worsen the outcome of the disease, as reported for other infections, as Pandemic Influenza A in 2009, SARS and MERS. In reverse, a Chinese report of 72,314 cases of COVID-19 patients showed a increase mortality rate of 7.3% in patients with pre existing diabetes as compared to 2.3% mortality rate that has been observed globally [51].

At present, COVID-19 infection in children and adolescents with type 1 diabetes is clinically different as compared to adults, without increased morbidity and mortality. Young patients with type 1 diabetes and COVID-19 infection usually don't need hospitalization, and careful management of glycometabolic assessment is required.

The localization of ACE2 receptors in the endocrine pancreas raises the question if COVID-19 infection is a risk factor for development of dysglycemia. A previous report showed that patients infected with SARS coronavirus - and not treated with glucocorticoids - showed transient hyperglycemia due to acute damage of beta cells induced by the virus, occurring within 3 days and 2 weeks after hospitalization [52].

Conflicting results have been reported about the role of ACE-inhibitors in COVID-19 infection: on one hand, ACE inhibitors may worsen the prognosis of severe pneumonia, on the other hand ACE inhibitors might reduce the severity of lung inflammation [53].

As for H1N1 viral infection as possible risk factor for diabetes, it has been reported that H1N1 strains are able to infect

and replicate in mammalian pancreatic cells both in vitro and in vivo, but are not associated with clinical onset of diabetes mellitus [54].

At present, there is no association between COVID-19 infection and the increased risk of type 1 diabetes: future studies are needed to better define the role of COVID-19 and autoimmunity.

The COVID-19 infection seems to be unusual among patients with type 1 diabetes mellitus, although they are considered a fragile population. It has been hypothesized that the peculiar immune condition that leads to the destruction of the beta cells might play an important role [55]. On the other hand, the risk of increased frequency of severe ketoacidosis in new-onset type 1 diabetes due to delayed diagnosis - because of fear of contracting COVID-19 in a hospital setting, or inability to contact a medical provider for timely evaluation - should be considered [56]. Similarly, parents of patients with poor glycemic control requiring closer follow-up might postpone the appointments for the same reasons.

Table 1 reports a summary of data extracted from studies looking at clinical characteristics of COVID-19 infection and its impact in patients affected by diabetes mellitus.

3.4. Adaptation of standard-of-care treatment regimens

Several pediatric diabetes centers have developed and implemented telemedicine services, thus allowing patients to remain in close contact with the team, to share glycemic data and insulin dosage, and to adapt disease management without close person-to-person contact, thus minimizing the risk of infection and of metabolic decompensation [57]. Benefit of telemedicine included prevention of ketoacidosis in long-standing patients thanks to remote monitoring [58]. In fact remote glycemic monitoring through cloud platforms has enabled pediatric diabetologists to obtain a closer interaction with patients during the pandemic lockdown. Thanks to telemedicine patients are now evaluated safely and more frequently, every week or two according to the degree of metabolic control. Telehealth is not only limited to glycemic control, but needs to be extended to all diabetic team, including diabetes educators, dieticians, psychologists [59].

Several pediatric teams with a dedicated dietician have prepared specific weekly food plans in order to prevent inappropriate excessive caloric intake, especially in this period of reduced physical exercise. On the other hand, promotion of physical exercise even during quarantine was followed by

Table 2 – General recommendations.

- Stay at home, avoid crowded places
- Wash your hands, don't touch eyes, nose and mouth
- Cover mouth and nose with bent elbow or tissue when coughing or sneezing
- Avoid contacts with other persons, particularly if affected by COVID-19
- Don't interrupt vaccination program.

Table 3 – ISPED practical recommendations for children and adolescents with type 1 diabetes.

- Reassure patients and families that consultations are available
- Maintain a good metabolic control, increase the glucose monitoring also by means of technological devices (i.e. pumps, continuous glucose monitoring, CGM)
- Improve telemedicine consultations for each component of the team
- Increase the use of CGM and remote monitoring
- Albeit outpatient section have reduced their activity, emergency section is always available in case of metabolic decompensation
- Promote adherence healthy nutrition, avoiding excessive caloric intake as well as minerals and oligoelements deficiency by increasing fruit and vegetable intake and reducing high-calorie food intake
- Patients treated with angiotensin converting enzyme (ACE)-inhibitors deserve attention
- In case of suspected symptoms, including difficult breathing or shortness of breath, persistent pain and chest pressure, immediately contact general practitioner and the hospital. Intensify blood glucose measurements and don't miss insulin administration, otherwise increase administration and corrective boluses as for other intercurrent illnesses
- Continue regular physical activity

an improvement of metabolic control [60]. Moreover, periodical teleconsult with psychologist has been guaranteed to help patients and families to cope with this stressful period and has been well accepted by both patients and families.

4. Patient education and psychological care

Type 1 diabetes is a chronic condition requiring complex clinical care and lifelong involvement, and may have significant influence not only on the physical and psychological but also on the emotional state in children, adolescents, and their caregivers. Intensive insulin treatment and new technological devices require patients and family engagement and significant modifications of daily life. Adequate food plan and exercise plan are mandatory to achieve and maintain good metabolic control. The observations based on the large number of infected people that were exposed and the evidence of person-to-person transmission of COVID-19 infection led to the social isolation of patients. Special attention and efforts to protect or reduce transmission have been applied in susceptible populations including children, especially if affected by chronic conditions like type 1 diabetes, health care providers, and fragile people. Elevated levels of stress, anxiety and depression have been reported during the outbreak, together with the fear of being infected, or infecting parents and relatives [61]. Even if COVID-19 infection in young patients with type 1 diabetes has been rarely encountered, patients experienced the awareness of being considered as a risk group. Moreover forced sedentary behavior might negatively influence exercise programs and degree of glycemic control [62]. Chewing and spitting out food as a compensatory behavior should be taken into account particularly if associated with weight gain and increased insulin requirement. Deterioration of metabolic control might also impair quality of life and resilience levels [63].

5. COVID-19 and pediatric diabetes: ISPED practical recommendations

Besides general recommendations for pediatric patients (Table 2), ISPED has proposed specific measures for patients with diabetes (Table 3).

Moreover, in case of COVID-19 infection, careful sick day management program proposed by International Society for Pediatric and Adolescents Diabetes (ISPAD) must be followed, together with specific treatment for the infection [64]. In case of hospitalization, a multidisciplinary management of the affected patients by strict cooperation between pediatric diabetologist and other physicians is mandatory. For adolescents with type 2 diabetes treated with metformin or other antidiabetic drugs, oral agents may need to be stopped, and insulin treatment considered for glucose control when hospitalized [65].

COVID-19 outbreak has removed many long-standing regulatory burdens to telehealth, and it is now assumed that telemedicine is a new safe and effective way for remote diabetes management [66].

Future research are needed to evaluate the impact of COVID-19 in type 1 diabetes mellitus patients, regarding not

only its hypothetical role in disease epidemiology, but also the implementation of new management strategies, the short- and long-term impact of telemedicine as current tool for diabetes care.

6. Organizational strategy for future scenarios

At present the recovery from COVID-19 pandemia is unpredictable, therefore the development of new alternative approaches to manage patients with diabetes is mandatory. The pandemia has removed several burdens to telehealth, and the use of universal digital platforms for continuous glucose monitoring download, as well as connectivity to electronic medical records deserve implementation. Telemedicine consultation improvement represents a new task for each component of the team, including physicians, nurses, dieticians, and psychologists.

COVID-19 pandemia represents a challenge for diabetologists in order to evaluate the consequences of this unpredictable scenario in diabetes mellitus, in particular regarding epidemiology, etiopathogenesis, management, psychological burden, quality of life. Multicenter studies are needed to increase the knowledge and to establish new prevention and therapeutic strategies.

7. Critical research priorities

1. Collect national real-data on the effects of lockdown and 2020 year infection rate on the metabolic and psychological outcomes of patients with type 1 diabetes
2. Determine the impact of the time of infection on weight, exercise activity and treatment regimens
3. Develop an epidemiological model to estimate the cumulative incidence of COVID-19 for patients with type 1 diabetes as well as the impact of the infection environment into the development of type 2 diabetes
4. Determine the COVID-19 morbidity in pregnant woman with long-term effects on glucose metabolism and prevalence of diabetes mellitus.

8. Conclusions (Sharing experience)

There is currently no evidence suggesting a higher risk of COVID-19 infection in children with diabetes than in unaffected peers. In addition, contrary to adult patients with diabetes, there are no reports suggesting that diabetes is a comorbidity associated with poor outcomes in children and adolescents. Despite the risk that the COVID-19 infection may develop into a more severe form seems to be lower if diabetes is well controlled, several practical recommendations may be useful. Children and adolescents affected by type 1 diabetes, as for other chronic conditions, need uninterrupted access to drugs, supplies, technology and care, especially in stressful situations. Since the lockdown reduced the access to outpatient clinics, pediatric diabetologists rescheduled all routine checks as telephone consultations and video-link consultations. In this stressful moment, patients and their families need to be reassured that a close link with the pediatric team is and will be available, and the medical care is

maintained and reinforced. Since strict glycometabolic control is mandatory to prevent short- and long-term complications, pediatric diabetologists realized the need to develop new and alternative routes for disease management. The reduction of direct contacts among patients and healthcare team might be responsible for the worsening of metabolic control, with an increased risk of severe decompensation, even if in absence of COVID-19 infection.

In Italy, both adult and pediatric scientific societies have obtained from the Italian Agency of Drugs (Agenzia Italiana del Farmaco, AIFA) that all patients with type 1 and type 2 diabetes can have access to drugs and self management without having to present the annual request form, that is usually released by diabetologists, limiting in this way the need to access hospitals.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

We gratefully thank Dr. Flavia Napoli MD for English revision.

Funding source

This research did not receive any specific grant from funding agencies in the public, commercial or not-profit sections.

REFERENCES

- [1] She Jiatong, Liu Wenjun. Epidemiological characteristics and prevention and control measures of Corona Virus Disease 2019 in children. *J Trop Medicine* 2020. ISSN 1672-3619, CN 44-1503/R.
- [2] World Health Organization. WHO characterizes COVID-19 as a pandemic. 1.1 (EB/OL)(2020-03-12)(2020-03-12).
- [3] Peeri NC, Shrestha N, Rahman MS, Zaki R, Tan Z, Bibi S, et al. The SARS, MERS and novel coronavirus (COVID-19) epidemics, the newest and biggest global health threats: what lessons have we learned?. *Int J Epidemiol* 2020;1–10. <https://doi.org/10.1093/ije/dyaa033>.
- [4] Del Rio C, Malani PN. COVID-19—New insights on a rapidly changing epidemic. *JAMA* 2020;323(14):1339–40.
- [5] Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk Factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med* 2020;13. <https://doi.org/10.1001/jamainternmed.2020.0994> e200994.
- [6] Lee PI, Hu YL, Chen PY, Huang YC, Hsueh PR. Are children less susceptible to COVID-19?. *J Microbiol Immunol Infect* 2020; S1684–1182(20):30039–46. <https://doi.org/10.1016/j.jmii.2020.02.011>.
- [7] Ludvigsson JF. Systematic review of covid-19 in children shows milder cases and a better prognosis than adults. *Acta Paediatr* 2020. <https://doi.org/10.1111/APA.15270>.
- [8] World Health Organization. Coronavirus disease 2019 (COVID-19): situation report 65; March 2020. <https://www.who.int/docs/default-source/coronaviruses/situation-reports/20200325-sitrep-65-covid-19.pdf>.
- [9] Italian National Health Institute (Istituto Superiore di Sanità). Coronavirus epidemic: situation report. March 26, 2020. [in Italian] https://www.epicentro.iss.it/coronavirus/bollettino/Bollettino-sorveglianza-integrata-COVID-19_26-marzo2020.pdf.
- [10] Wei M, Yuan J, Liu Y, Fu T, Yu X, Zhang ZJ. Novel coronavirus infection in hospitalized infants under 1 year of age in China. *J Am Med Assoc* 2020. <https://doi.org/10.1001/jama.2020.2131>.
- [11] Hong H, Wang Y, Chung HT, Chen CJ. Clinical characteristics of novel coronavirus disease 2019 (COVID-19) in newborns, infants and children. *Pediatr Neonatol* 2020. <https://doi.org/10.1016/j.pedneo.2020.03.001>.
- [12] Egloff C, Vauloup-Fellous C, Picone O, Mandelbrot L, Roques P. Evidence and possible mechanisms of rare maternal-fetal transmission of SARS-CoV-2. *J Clin Virol* 2020. <https://doi.org/10.1016/j.jcv.2020.104447>.
- [13] Qiu H, Wu J, Hong L, Luo Y, Song Q, Chen D. Clinical and epidemiological features of 36 children with coronavirus disease 2019 (COVID-19) in Zhejiang, China: an observational cohort study. *Lancet Infect Dis* 2020;S1473–3099 (20):30198–205. [https://doi.org/10.1016/S1473-3099\(20\)30198-5](https://doi.org/10.1016/S1473-3099(20)30198-5).
- [14] Xia W, Shao J, Guo Y, Peng X, Li Z, Hu D. Clinical and CT features in pediatric patients with COVID-19 infection: different points from adults. *Pediatr Pulmonol* 2020;1–6. <https://doi.org/10.1002/ppul.24718>.
- [15] Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, et al. Genomic characterization and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet* 2020;395:565–74. [https://doi.org/10.1016/S0140-6736\(20\)30251-8](https://doi.org/10.1016/S0140-6736(20)30251-8).
- [16] Parri N, Lenge M, Buonsenso D for the Coronavirus Infection in Pediatric Emergency Departments (CONFIDENCE) Research Group. Children with Covid-19 in pediatric emergency departments in Italy. *NEJM* 2020, May 1. doi: 10.1056/NEJMc2007617.
- [17] Muller LM, Gorter KJ, Hak E, Goudzwaard WL, Schellevis FG, Hoepelman AI, et al. Increased risk of common infections in patients with type 1 and type 2 diabetes mellitus. *Clin Infect Dis* 2005;41(3):281–8. <https://doi.org/10.1086/431587>.
- [18] Critchley JA, Carey IM, Harris T, DeWilde S, Hosking FJ, Cook DG. Glycemic control and risk of infections among people with type 1 or type 2 diabetes in a large primary care cohort study. *Diabetes Care* 2018;41:2127–35. <https://doi.org/10.2337/dc18-0287>.
- [19] Ma CM, Yin FZ. The mortality in infectious in patients with type 2 diabetes compared with non-diabetic population: Infection in type 2 diabetes. *Medicine (Baltimore)* 2019;98(24). <https://doi.org/10.1097/MD.00000000000016025> e16025.
- [20] Zoppini G, Fedeli U, Schievano E, Dauriz M, Targher G, Bonora E, et al. Mortality from infectious diseases in diabetes. *Nutr Metab Cardiovasc Dis* 2018;28:444–50. <https://doi.org/10.1016/j.numecd.2017.12.007>.
- [21] Casqueiro J, Casqueiro J, Alves C. Infections in patients with diabetes mellitus: a review of pathogenesis. *Indian J Endocrinol Metab* 2012;16(S1):S27–36. <https://doi.org/10.4103/2230-8210.94253>.
- [22] Akirov A, Diker-Cohen T, Masri-Iraqi H, Duskin-Bitan H, Shimon I, Gorshtein A. Outcomes of hyperglycemia in patients with and without diabetes hospitalized for infectious diseases. *Diabetes Metab Res Rev* 2018;34(7). <https://doi.org/10.1002/dmrr.3027> e3027.
- [23] Burekovic A, Dizdarevic-Bostandzic A, Godinjak A. Poorly regulated blood glucose in diabetic patients-predictor of acute infections. *Med Arch* 2014;68:163–6. <https://doi.org/10.5455/medarh.2014.68.163-166>.

- [24] Del Roio jr LR, Barbosa SFC, das Gracias Alkimin M, Bellinati-Pires R, Florido MPC, Isaac L, et al. Is immunity in diabetic patients influencing the susceptibility to infections? Immunoglobulins, complement and phagocytic function in children and adolescents with type 1 diabetes mellitus. *Pediatr Diabetes* 2005;6:206–12. <https://doi.org/10.1111/j.1399-543X.2005.00136.x>.
- [25] Hyöty H. Viruses in type 1 diabetes. *Pediatr Diabetes* 2016;17 (Suppl 22):56–64. <https://doi.org/10.1111/vedi.12370>.
- [26] Rodriguez-Calvo T. Enteroviral infections as a trigger for type 1 diabetes. *Curr Diab Rep* 2018;18(11):106. <https://doi.org/10.1007/s11892-018-1077-2>.
- [27] Toniolo A, Cassani G, Puggioni A, Rossi A, Colombo A, Onodera T, et al. The diabetes pandemic and associated infections: suggestions for clinical microbiology. *Rev Med Microbiol* 2019;30:1–17. <https://doi.org/10.1097/MRM.0000000000000155>.
- [28] Ramondetti F, Sacco S, Comelli M, Bruno G, Falorni A, Iannilli A, et al. Type 1 diabetes and measles, mumps and rubella childhood infections within the Italian Insulin-dependent Diabetes Registry. *Diabet Med* 2012;29:761–6. <https://doi.org/10.1111/j.1464-5491.2011.03529.x>.
- [29] Maines E, Franceschi R, Cauvin V, d'Annunzio G, Pini Prato A, Castagnola E, et al. Iliopsoas abscess in adolescents with type 1 diabetes mellitus. *Clin Case Rep* 2015;3:638–42. <https://doi.org/10.1002/ccr3.267>.
- [30] Bazmamoun H, Rafeey M, Nikipuori M, Ghergherehchi R. *Helicobacter pylori* infection in children with type 1 diabetes: a case control study. *JHRS* 2016;16:68–71.
- [31] Zubair KU, Shah AH, Fawwad A, Sabir R, Butt A. Frequency of urinary tract infection and antibiotic sensitivity of uropathogens in patients with diabetes. *Pak J Med Sci* 2019;35:1664–8. <https://doi.org/10.12669/pjms.35.6.115>.
- [32] Lachmandas E, Thiem K, van den Heuvel C, Hijmans A, de Galan BE, Tack CJ, et al. Patients with type 1 diabetes mellitus have impaired IL-1 β production in response to *Mycobacterium tuberculosis*. *Eur J Clin Microbiol Infect Dis* 2018;37:371–80. <https://doi.org/10.1007/s10096-017-3145-y>.
- [33] Pawłowicz M, Birkholz D, Niedzwiecki M, Balcerska A. Difficulties or mistakes in diagnosing type 1 diabetes in children?—demographic factors influencing delayed diagnosis. *Pediatr Diabetes* 2009;10:542–9. <https://doi.org/10.1111/j.1399-5448.2009.00516.x>.
- [34] Korbel L, Easterling RS, Punja N, Spencer JD. The burden of common infections in children and adolescents with diabetes mellitus: a Pediatric Health Information System study. *Pediatr Diabetes* 2018;19:512–9. <https://doi.org/10.1111/vedi.12594>.
- [35] American Diabetes Association. Standards of medical care in diabetes—2012. *Diabetes Care* 2012;35(Suppl 1):S11–63.
- [36] Morgan E, Halliday SR, Campbell GR, Cardwell CR, Patterson CC. Vaccinations and childhood type 1 diabetes mellitus: a meta-analysis of observational studies. *Diabetologia* 2016;59:237–43. <https://doi.org/10.1007/s00125-015-3800-8>.
- [37] Verger P, Bocquier A, Vergélys C, Ward J, Peretti-Watel P. Flu vaccination among patients with diabetes: motives, perceptions, trust, and risk culture - a qualitative survey. *BMC Public Health* 2018;18:569. <https://doi.org/10.1186/s12889-018-5441-6>.
- [38] Arrelias CC, Bellissimo-Rodrigues F, Lima LC, Silva AS, Lima NK, Zanetti ML. Hepatitis B vaccination coverage in patients with diabetes mellitus. *Rev Esc Enferm USP* 2016;50:255–62. <https://doi.org/10.1590/S0080-623420160000200011>.
- [39] Eisenhut M, Chesover A, Misquith R, Nathwani N, Walters A. Antibody responses to immunizations in children with type 1 diabetes mellitus: a case-control study. *Clin Vaccine Immunol* 2016;23:873–7. <https://doi.org/10.1128/CVI.00400-16>.
- [40] Wolkers PCB, Yakuwa MS, Pancieri L, Mendes-Rodrigues C, Furtado MCC, Mello DF. Children with type 1 diabetes mellitus: access to special immunobiological and child care. *Rev Esc Enferm USP* 2017;9(51). <https://doi.org/10.1590/S1980-220X2016049103249> e03249.
- [41] Elding Larsson H, Lynch KF, Lönnrot M, Haller MJ, Lernmark Å, Hagopian WA, et al. TEDDY Study Group. Pandemrix® vaccination is not associated with increased risk of islet autoimmunity or type 1 diabetes in the TEDDY study children. Version 2. *Diabetologia* 2018;61:193–202. <https://doi.org/10.1007/s00125-017-4448-3>.
- [42] Principi N, Iughetti L, Cappa M, Maffei C, Chiarelli F, Bona G, et al. Italian Pneumococcal Study Group on Diabetes. *Streptococcus pneumoniae* oropharyngeal colonization in school-age children and adolescents with type 1 diabetes mellitus: Impact of the heptavalent pneumococcal conjugate vaccine. *Hum Vaccin Immunother* 2016;12:293–300. <https://doi.org/10.1080/21645515.2015.1072666>.
- [43] Rabbone I, Scaramuzza AE, Iafusco D, Bonfanti R, Lombardo F, Cherubini V, et al. Pandemic influenza vaccination coverage in children with type 1 diabetes: analysis from seven Italian centers. *Hum Vaccin* 2011;7(12):1291–2. <https://doi.org/10.4161/hv.7.12.18335>.
- [44] Shenoy A, Ismaili M, Bajaj M. Diabetes and Covid-19: a global health challenge. *BMJ Open Diab Res Care* 2020;8. <https://doi.org/10.1136/bmjdr-2020-001450> e001450.
- [45] Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan China: a descriptive study. *Lancet* 2020;395(10223):507–13. [https://doi.org/10.1016/S0140-6736\(20\)30211-7](https://doi.org/10.1016/S0140-6736(20)30211-7).
- [46] Guo W, Li M, Dong Y, Zhou H, Zhang Z, Tian C, et al. Diabetes is a risk factor for the progression and prognosis of COVID-19. *Diabetes Metab Res Rev* 2020:e3319. <https://doi.org/10.1002/dmrr.3319>.
- [47] Muniyappa R, Gubbi S. Perspective COVID-19 pandemic, coronaviruses, and diabetes mellitus. *Am J Physiol Endocrinol Metab* 2020;318(5):E736–41. <https://doi.org/10.1152/ajpendo.00124.2020>.
- [48] Wysocki J, Ye M, Soler MJ, Gurley SB, Xiao HD, Bernstein KE, et al. ACE and ACE2 activity in diabetic mice. *Diabetes* 2006;55:2132–9. <https://doi.org/10.2337/db06-0033>.
- [49] Fernandez C, Rysa J, Almgren P, Nilsson J, Engstrom G, Orho-Melander M, et al. Plasma levels of the proprotein convertase furin and incidence of diabetes and mortality. *J Intern Med* 2018;284:377–87. <https://doi.org/10.1111/joim.12783>.
- [50] Fadini GP, Morieri ML, Longato E, Avogaro A. Prevalence and impact of diabetes among people infected with SARS-CoV-2. *JEI* 2020. <https://doi.org/10.1007/s-40618-020-01236-2>.
- [51] Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72314 cases from the Chinese center for disease control and prevention. *J Am Med Ass* 2020. <https://doi.org/10.1001/jama.2020.2648>.
- [52] Yang JK, Lin SS, Ji XJ, Guo LM. Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes. *Acta Diabetol* 2010;47:193–9. <https://doi.org/10.1007/s00592-009-0109-4>.
- [53] Bavishi C, Maddox TM, Messerli FH. Coronavirus disease (COVID-19) infection and renin angiotensin system blockers. *JAMA Cardiol* 2020. <https://doi.org/10.1001/jamacardio.2020.1282>.
- [54] Capua I, Mercalli A, Romero-Tejeda A, Pizzuto MS, Kasloff S, Sordi V, et al. Study of 2009 H1N1 pandemic influenza virus as a possible causative agent of diabetes. *J Clin Endocrinol Metab* 2018;103:4343–56. <https://doi.org/10.1210/je.2018-00862>.

- [55] Tatti P, Tonolo G, Zanfardino A, Iafusco D. The CoV-19 infection appears to be unusual among patients with type 1 diabetes mellitus, although they are considered a fragile population. We think that this in part due to the peculiar immune condition that leads to the destruction of the beta cells. *Med Hypotheses* 2020;29(142). <https://doi.org/10.1016/j.mehy.2020.109795> 109795.
- [56] Cherubini V, Gohil A, Addala A, Zanfardino A, Iafusco D, Hannon T, et al. Unintended consequences of COVID-19: Remember general pediatrics. *J Pediatrics* 2020;223:197–8. <https://doi.org/10.1016/j.jpeds.2020.05.004>.
- [57] Nørgaard C. Telemedicine consultations and diabetes technology during COVID-19. *J Diabetes Sci and Technol* 2020. <https://doi.org/10.1177/1932296820929378>.
- [58] Peters AL, Garg S. The silver lining to COVID-19: Avoiding diabetic ketoacidosis admissions with telehealth. *Diab Technol Ther*. 2020;22(6). <https://doi.org/10.1089/dia.2020.0187>.
- [59] Jones MS, Goley 1 AL, Alexander BE, Keller BE, Caldwell MM, Buse JB. Inpatient transition to virtual care during covid-19 pandemic. *Diab Technol Therap* 2020;22(6). <https://doi.org/10.1089/dia.2020.0206>.
- [60] Tornese G, Ceconi V, Monasta L, Carletti C, Faleschini E, Barbi E. Glycemic control in type 1 diabetes mellitus during covid-19 quarantine and the role of in-home physical activity. *Diab Technol Therap* 2020;22(6). <https://doi.org/10.1089/dia.2020.0169>.
- [61] Wang C, Pan R, Yilin Tan X, Xu L, Ho C, Ho RC. Immediate psychological responses and associated factors during the initial stage of the 2019 coronavirus disease (COVID-19) epidemic among the general population in China. *Int J Environ Res Public Health* 2020;17(5):1729. <https://doi.org/10.3390/ijerph17051729>.
- [62] Hall G, Laddu DR, Phillips SA, Lavie CJ, Arena R. A tale of two pandemics: How will COVID-19 and global trends in physical inactivity and sedentary behavior affect one another?. *Prog Cardiovasc Dis* 2020;S0033–0620(20):30077–83. <https://doi.org/10.1016/j.pcad.2020.04.005>.
- [63] Lukács A, Mayer K, Sasvári P, Barkai L. Health-related Quality of Life of adolescents with type 1 diabetes in the context of resilience. *Pediatr Diab* 2018;19(8):1481–6. <https://doi.org/10.1111/pedi.12769>.
- [64] Laffel LM, Limbert C, Phelan H, Virmani A, Wood J, Hofer SE. ISPAD clinical practice consensus guidelines 2018: Sick day management in children and adolescents with diabetes. *Pediatr Diabetes* 2018;19(Suppl 27):193–204. <https://doi.org/10.1111/pedi.12741>.
- [65] Gupta R, Ghosh A, Singh AK, Misra A. Clinical considerations for patients with diabetes in times of COVID-19 epidemic. *Diabetes Metab Syndr* 2020;14:211–2. <https://doi.org/10.1016/j.dsx.2020.03.002>.
- [66] Garg SK, Rodbard D, Hirsch IB, Forlenza GP. Managing new-onset type 1 diabetes during the COVID-19 pandemic: challenges and opportunities. *Diab Technol Therap* 2020;22(6). <https://doi.org/10.1089/dia.2020.0161>.