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.

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Review

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

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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.

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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.

Contents

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, treatment 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. Lancet 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 chronicle 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. J Am Med Ass 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. Diabetes Metab Syndr 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. JEI 2020; htpps://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).

March 31st, 2020 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.	Research article. Retrospective study on 174 adult patients, admitted from 10th to 29th February 2020.	To define whether diabetes influences COVID-19 infection.	Diabetes is a risk factor for rapid progression and bad prognosis of COVID-19 pneumonia.
March 31st, 2020 Muniyappa R, Gubbi S. Perspective: COVID-19 pandemic, coronaviruses, and diabetes mellitus. Am J Physiol Endocrinol Metab 2020 May 1; 318(5): E736–E741 [46]	Research article. Pathophysiology study.	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.	Importance of identification of clinical and biochemical parameters using multiomics approaches, that predict severity of COVID-19 in patients with diabetes.
April 17th, 2020 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):1–9. [66]	Original article	To define the role of telemedicine in type 1 diabetes management	Telemedicine in an effective approach for the management of new-onset type 1 diabetes particularly during COVID-19 pandemia

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 i ntake 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 electronical 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.

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