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COVID-19 and Type 1 Diabetes: Concerns and Challenges

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Summary: Due to the current COVID-19 pandemic, worldwide population's lifestyle has changed dramatically, causing psychosocial consequences. Patients presenting a preexisting chronic condition, as Type 1 Diabetes (T1D), are the ones suffering the most from this situation. Moreover, people affected by diabetes are the ones with the worst prognosis, if infected by SARS-CoV-2. We analyzed why patients with T1D were poorly represented between the subjects hospitalized for COVID-19 and why the cases of diabetic ketoacidosis (DKA) were fewer and more severe compared with the past years. Furthermore, literature has showed how patients of all ages with T1D did not experience a deterioration in their glucose control throughout the lockdown. Among other causes, this is also due to the surging use of telemedicine. Finally, we tried to understand how the coronavirus tropism for endocrine tissues could influence the future epidemiology of T1D, focusing on the effects they have on pancreatic β-cells.

Key words: COVID19, Type 1 Diabetes, Children, Telemedicine

Background

In December 2019 in Wuhan, Hubei province, China, a new infection disease began to spread: Coronavirus Disease 2019 (COVID-19). The disease, caused by the Severe Acute Respiratory Syndrome CoronaVirus 2 (SARS-CoV-2), rapidly increased worldwide, causing thousands of deaths.

The World Health Organization declared the outbreak a Public Health Emergency of International Concern on January 30, 2020 (1), and a pandemic on March 11, 2020 (2).

The clinical picture of the infection has an extreme variability: it goes from asymptomatic patients or mild forms with fever, cough, fatigue, and loss of smell and taste, to severe cases ending up in ICU for an Acute Respiratory Distress Syndrome (ARDS). This is due to a ripple effect caused by a cytokine storm that may lead to multi-organ failure, septic shock, or thrombosis. Since the beginning of the pandemic, COVID-19 caused a significant concern for the possible consequences in patients presenting a preexisting chronic condition, such as diabetes (3). Moreover, the pandemic was a major challenge to both diagnosis and treatment at the onset and in the follow-up of Type 1 Diabetes (T1D).

In this short review, we update the relevant concerns and challenges of COVID-19 in T1D patients, namely in children and adolescents.

Methods

A literature search was conducted using PubMed. The terms used were COVID-19 OR coronavirus AND Type 1 Diabetes and as filter all articles about pediatric and adolescent population were included.

Most of the publications were single case reports, small case series, original articles, letters or literature reviews.

Do All Patients With Diabetes are at Risk for COVID-19?

The epidemiological studies clearly show that the prevalence of subjects with diabetes affected by COVID-19 is not different from the prevalence of diabetes in the general population (4-7). However, diabetes has been identified as an important risk factor for higher mortality and higher rate of progression to acute respiratory distress syndrome in hospitalized patients with COVID-19. In particular, the vast majority of the more severe COVID-19 diabetic patients are adults affected by type 2 diabetes. This is due to the preexistence of micro and macrovascular complications (5).

Patients with T1D are poorly represented among the subjects hospitalized for COVID-19 (5,6); however, this same demographic is way more represented in hospitalized cases than in the general population (1.5% vs 0.4% respectively) (7).

This peculiarity brought to a series of hypotheses. For instance, this may be due to the lower prevalence of the COVID-19 among younger people, and to the fact that T1D is majorly present in younger individuals (8).

Moreover, the limited involvement of patients with T1D in this pandemic may be probably caused by their alertness to the evolving situation and the precautionary approach they had as carriers of a chronic condition (9).

Nevertheless, these hypotheses cannot fully explain the data since, as said by Tatti et al. (10), there are not comparative cases in a T1D adult population. Furthermore, the spreading of the virus mainly happened after several policies were applied by Italy and many other countries, ranging from social distancing measures to flights' shutdown.

On the other hand, it would be rather important to focus on the genetic and immunological basis of autoimmune diabetes. First of all, because the subjects with T1D share a common genetic background. Secondly, the milder course of the disease in Type 1 Diabetes cases could be explained by an imbalance between Th1 and Th2 immunity (11). This immunological pattern causes insulitis in subjects with TID. In fact, the Th1 immunity is mainly proinflammatory and acts against pathogens, internalizing them, and this may be the case of SARS-CoV-2.

This hypothesis could also explain why children and adolescents usually experience a milder course of the COVID-19 disease. In younger individuals, the prevalence of Th1 immunity is predominant against the Th2 immunity, which is mediated by B-lymphocytes and antibodies (12).

DKA in COVID-19 Pandemic

Diabetic ketoacidosis (DKA) is a common and potentially lethal acute onset scenario or a complication of diabetes caused by a relative or absolute insulin deficiency. DKA occurs frequently in different occasions: at the onset of the disease, when the patient misses the doses of insulin, or in the setting of another moderate to severe illness.

This process generates an inflammatory state (producing pro-inflammatory cytokines, IL-6, TNFα and IL-β) which can be sometimes accompanied by an underlying illness.

Looking at previous research on coronaviruses, it has been demonstrated that SARS-CoV-1 binds the Angiotensin-Converting Enzyme 2 (ACE2) receptor in the pancreatic islets. The binding between the viruses and the receptors provokes a damage of the islets leading to acute diabetes (13). This happens also for SARS-CoV-2 (14).

Moreover, it is important to notice how COVID-19 patients with a severe disease, have high levels of inflammatory markers such as IL-6. The inflammatory cascades of the two pathologies (COVID-19 and T1D) may act synergistically leading to a worse outcome.

The Italian Society for Pediatric Endocrinology and Diabetes (ISPED) evaluated the changing of frequencies of DKA, clinical conditions at diagnosis, and acute complications in the early phase of COVID-19 in people with T1D (15). Data show that, during the observation, the new onsets of T1D are less than those in the same period of 2019. On the other hand, children with DKA presented a more severe form of DKA than in 2019.

The decreased number of T1D onsets can be the result of the fear of COVID-19. A recent survey in Emilia-Romagna region (Italy) clearly showed a consistent drop in attendances at the Pediatric Emergency Unit during the COVID-19 epidemic (16) increasing the risk of delayed diagnoses of potentially severe disease, like T1D. Moreover, this is also caused by a lower exposure to seasonal viruses, since one of the first social distancing measures adopted by the Italian government concerned the shutdown of schools.

Furthermore, the possible delayed diagnosis of T1D could also explain the increase of severe DKA registered, alongside the effects of SARS-CoV-2 on β-cells (13).

A study by Ebekozien et al. (17) shows that DKA is the most prevalent adverse outcome in patients with COVID-19 disease, in addition to hyperglycemia. Moreover, COVID-19 symptoms can mask the onset of DKA (18) delaying the diagnosis.

As a final consideration, all data analyzed push to improve the prevention of DKA carrying out specific campaigns for parents and doctors, as it occurred in Italy with the help of the Scientific Societies and Patients Associations.

Glycemic Control in Adults and Children With Type 1 Diabetes During the Lockdown

During the pandemic, most countries issued strict governmental decrees that imposed social distancing and isolation to avoid and minimize community-based viral transmission. Indeed, the Italian government was one of the firsts to impose a lockdown restriction from March 9 to May 3, 2020 (19). These measures gradually reduced the cases of infection but changed completely the lifestyle of the inhabitants.

The lockdown period and the change in lifestyle may have been affecting the psychosocial health of the population. In fact, those affected by a chronic illness presented a major risk (20): people affected by T1D were unable to continue their routinely follow-up and they were obliged to modify the management of their chronic disease.

Despite this unexpected change of lifestyle, all the studies published until now show that patients of all ages with T1D did not experience deterioration in their glucose control during lockdown.

Bonora et al. (21) analyzed a group of adult patients affected by T1D who was using a FGM system during the period of lockdown and the weeks before it. They observed that glucose control improved (increasing the Time In Range and reducing average glucose) during the first week of lockdown. The authors emphasized that the slowdown of the routine activities has a favorable effect on glucose control. This is probably due to the more regular lifestyle, the more time composing meals, and the risk awareness of more severe COVID-19 complications. Confirming this hypothesis, the control group including patients who continued their work routine did not show an improvement in their glycemic control.

Moreover, Schiaffini et al (22) analyzed a group of pre-school and school children that utilize a tandem basal bolus IQ. This demographic showed a better metabolic performance improving the glycemic Time In Range, and reducing the glycemic Time Above Range. What probably makes the difference on the management of diabetes at this age is the shift to a full-time parental control: parents control more often glycemic levels, adapt insulin management, and prepare meals in a more accurate way.

Adolescents also showed a good glycemic control at baseline, and they did not worsen during the first weeks of lockdown; improving the time in glycemic range and reducing the time below the range in the following weeks. Furthermore, the period of lockdown had no pejorative effects on the metabolic control on this demographic. These results in adolescents are probably due to the exclusion of the influence played by some school and after-school activities, eating every meal at home, and in-home physical activities (23).

Confirming this hypothesis, an Italian web-based pediatric survey analyzed the changing of lifestyle in patients with Type 1 Diabetes during the quarantine period due to COVID-19 (24). It showed how >12-year-old patients reported having practiced indoor physical activities regularly during the lockdown: regular exercise is fundamental even for psychological wellbeing, since it reduces anxiety and it improves the general mood and the quality of sleep (25). While <12-year-old patients monitored glycemic levels more often, probably because of the higher parental control during the "stay at home" policy.

The Role of Telemedicine

In this lockdown period, routinely medical activities were near totally reduced to enlarge the ICU capacity and minimize the social activities among people if not strictly necessary. People with a chronic illness would have been deprived by their follow-up checkups, if it were not for telemedicine.

Telemedicine offers a way to be close to patients with T1D, even during the pandemic, as physical proximity is not always necessary.

Nowadays technology plays an important role in diabetic management. A large percentage of patients with T1D and parents handle regularly continuous or fast glucose monitoring and the insulin pump. Most of the data collected by these instruments can be remotely analyzed by the doctor, who can suggest and discuss with the patient the management of the glycemic control.

This new medical approach has been largely used during the pandemic with good results as reported above (21,23): even if the rapid improvement of telemedicine has been the only viable way in the pandemic, we think that it could be integrated in the business-as-usual care of T1D in the aftermath. In fact, telemedicine is more sustainable: it gives a better continuity of the assistance and healthcare; it fastens and simplifies the communication between doctors and patients.

Furthermore, also past years' studies showed how telemedicine is a proven modality to prevent DKA in adolescents and an effective tool for diabetes care (26, 27). Moreover, at the onset of diabetes, the start of an insulin treatment and education should not be postponed, so during the pandemic, when it was not possible to educate people in medical structures, teleconferencing was a valid alternative. However, telemedicine raises new issues, such as a privacy one (28).

Can COVID-19 Change the Epidemiology of T1D?

It is known that viral infections have been widely associated with the T1D pathogenesis. In 2017, the TEDDY study (30) proved an increased risk of β-cells autoimmunity in a group of patients that recently experienced a respiratory infection caused by a range of different pathogens, including Coronavirus.

The mechanisms at the basis of the autoimmune insulitis are different: the amplification of viruses or the diffusion of viral antigens in the circulation can determine an immune response involving pancreatic cells; a direct damage of β-cells may release sequestered islet antigens; viral epitopes sharing homologies with autoantigens leading to the production of cross-reactive antibodies against β-cells; a viral infection promotes cytokine releasing and T-cell activation in individuals genetically predisposed to autoimmunity contributing to the faster development of diabetes (30).

Moreover, as anticipated, SARS-CoV-2 binds the ACE2 receptors, which are expressed in metabolic organs and tissues (pancreatic β-cells, adipose tissue, small intestine, and kidneys). Therefore, it is possible that the virus alters the glucose metabolism and that it could complicate the pathophysiology of preexisting diabetes or lead to new mechanisms of the disease and to an onset of diabetes (31).

So, given that T1D has already been related to coronavirus respiratory infections and knowing what happened after the SARS-CoV-1 pandemic in 2003, we can infer that something similar could happen in the future. A recent case of a young woman developing an autoimmune T1D one month after getting affected by COVID-19 support this hypothesis (32).

It is plausible to presume that the pandemic will trigger an increase of T1D cases during the next months/years, especially in people infected by

SARS-CoV-2 that are genetically predisposed to diabetes (33).

Conclusions

COVID-19 pandemic continues to be a concern for doctors since it is well known it can be particularly severe for T1D-patients, leading to a more complicate scenario, increasing the mortality risk. Therefore, SARS-CoV-2 can impair also the DKA presentation. During the quarantine, the cases of DKA were less numerous, but more severe than the ones in the last years.

However, the challenge in the management of the disease is successfully raising attention to the meal composition and improving the metabolic control due to the constant presence of parents during the day, particularly in the pre-school and school children. Even the adolescents, especially the ones who practice physical activity at home, demonstrated a better glycemic control.

Telemedicine was fundamental and probably simplified the relationship between the doctor and the patient, bringing them closer. In addition, the "stay at home" policy brought light to the management of diabetes as a priority to tackle during the lockdown.

To conclude, the effects of the virus on the endocrine pancreatic tissue remain a pending issue. We cannot exclude a "second wave" of onsets of T1D due to the viral trigger of SARS-CoV-2.

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

References

1. Statement on the second meetting of the International Health Regulations (200%) Emergency Committee regarding the outbreak of novel coronavirus (2019-nCoV). World Health Organozation (WHO) (Press release). 30th Janaury 2020. Archived from the original on 31st January 2020. Retrieved 30th January 2020. https://www.who.int/news-room/detail/30-01-2020-statement-on-the-second-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-outbreak-of-novel-coronavirus-(2019-ncov) last access July 30, 2020
2. WHO Director-General's opening remarks at the briefing on COVID-19 – 11th March 2020. World Health Organization (WHO) (press release). 11th March 2020. Archieved from the original on 11th March 2020. Retrieved 12th March 2020. https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020 last access July 30, 2020
3. Centers for Disease Control and Prevention. National Diabetes Statistics Report, 2020. Atlanta, GA: Centers for Disease Control and Prevention, US Department of Health and Human Services; 2020.
4. Selvin E, Juraschek SP. Diabetes Epidemiology in the COBID-19 Pandemic. Diabetes Care, 2020; 43(8):1690–1694.
5. Apicella M, Campopiano MC, Mantuano M, Mazoni L, Coppelli A, Del Prato S. COVID-19 in people with diabetes: understanding the reasons for worse outcomes. Lancet Diabetes Endocrinol. 2020 Sept;8(9):782-792
6. Huang I, Lim MA, Pranata R. Diabtetes mellitus is associated with increased mortality and severity of disease in COVID-19 pneumonia e A systematic review, meta analysis, and meta-regression. Diabetes Metab Syndr 2020; 14:395-403
7. Barron E, Bakhai C, Kar P et al. Type 1 and Type 2 diabetes and COVID-19 related mortality in England: a whole population study. https://www.england.nhs.uk/wp-content/uploads/2020/05/Valabhji-COVID-19-and-Diabetes-Paper-2-Full-Manuscript.pdf
8. Pitocco D, Tartaglione L, Viti L et al. Lack of Type 1 Diabetes involvement in SARS-CoV-2 population: Only a particular coincidence? Diabetes Res Clin Pract. 2020; 164:108220
9. Bronson SC. Letter to the Editor in response to the article "Lack of Type 1 Diabetes involvement in the SARS-CoV-2 population: Only a particular coincidence?". Diabetes Res Clin Pract, 2020; 3:108306
10. Tatti P, Tonolo G, Zanfardino A, Iafusco D. Letter to the Editor: CoVid-19 and Type 1 Diabetes: Every cloud has a silver lining. Searching the reason of a lower aggressiveness of the CoronaVirus disease in Type 1 Diabetes. Diabetes Res Clin Pract. 2020 Jun 12:108270. doi: 10.1016/j.diabres.2020.108270. Online ahead of print
11. Tatti P, Tonolo G, Zanfardino A, Iafusco D. Is it fair that patients with Type 1 Diabetes (autoimmune) may be spared by the infection of Covid-19? Medical Hypothesis 2020;14: 109795
12. Fallahi P, Ferrari SM, Ragusa F et al. Th1 chemokines in autoimmune endocrine disorders. J Clin Endocrinol Metab 2020;105(4):dgz289. doi: 10.1210/clinem/dgz289
13. Yang JK, Lin SS, Ji XJ, Guo LM. Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes. Acta Diabetol. 2010;47:193–199.
14. Yang L, Han Y, Nilsson-Payant BE, et al. A human pluripotent stem cell-based platform to study SARS-CoV-2

tropism and model virus infection in human cells and organoids. Cell Stem Cell 2020; 27(1):125–136.e7
15. Rabbone I, Schiaffini R, Cherubini V et al. Has COVID-19 delayed the diagnosis and worsened the presentation of typer 1 diabetes in children? Diabetes Care, 2020 Online Ahead of Print
16. Cella A, Marchetti F, Iughetti L et al. Italian COVID-19 epidemic: effects on paediatric emergency attendance—a survey in the Emilia Romagna region. FREE BMJ Paediatrics Open 2020, 4 (1) e000742
17. Ebekozien OA, Noor N, Gallagher MP , Todd Alonso G. Type 1 Diabetes and COVID-19: preliminary findings from a multicenter surveillance study in the U.S. Diabetes Care, 2020; 43(8):e83–e85
18. Potier L, Julla JB, Roussel R et al. COVID-19 symptoms masking inaugural ketoacidosis of Type 1 Diabetes. Diabetes Metab, 2020; S1262–3636(20)30081
19. Buonsenso D, Onesimo R, Valentini P et al. Children's healthcare during corona virus disease 19 Pandemic: the Italian Experience. Pediatr Infect Dis J. 2020; 39:e137–40.
20. Wang C, Pan R, Wan X et al. Immediate psychosocial 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
21. Bonora BM, Boscari F, Avogaro A. Glycaemic control among people with Type 1 Diabetes during lockdown for the SARS-CoV-2 outbreak in Italy. Diabetes Ther, 2020, 11:1369–1379
22. Beato-Vibora PI. No deleterious effect of lockdown due to COVID-19 pandemic on glycaemic control, measured by glucose monitoring, in adults with Ttype 1 diabetes. Diabetes Technology and Therapeutics, 2020. DOI: 10.1089
23. Schiaffini R, Barbetti F, Rapini N et al. School and preschool children with Type 1 Diabetes during COVID-19 quarantine: the synergic effect of parental control and technology. Diabetes Res Clin Pract, 2020;108302
24. 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. Diabetes Tech and Therap, 2020; 22:6.
25. Passanisi S, Pecoraro M, Pira F et al. Quarantine due to the COVID-19 pandemic from the perspective of pediatric patients with Type 1 Diabetes: a web-based survey. Frontiers in Pediatrics, 2020; 8:491
26. Peluso MA, Guerra de Andrade LH. Physical activity and mental health: the association between exercise and mood. Clinics (Sao Paulo) 2005; 60:61–70
27. Wagner DV, Barry SA, Stoeckel M et al. NICH at its best for diabetes at its worst: texting teens and their caregivers for better outcomes. J Diabetes Sci Technol, 2017;11:468–475
28. McDonnel ME. Telemedicine in complex diabetes management. Curr Diab Rep. 2018; 18:42
29. Ziegler R. Challenges in the Care of Children and Youth With Diabetes in Times of the Corona Pandemic: Personal View of the Situation in a German Clinic. J Diabetes Sci Technol. 2020;14:811–812.
30. Lönnrot M, Lynch KF, Elding Larsson H et al. Respiratory infections are temporally associated with initiation of Type 1 Diabetes autoimmunity: the TEDDY study. Diabetologia 2017; 60:1931–40
31. Op de Beeck A, Eizirik DL. Viral infections in Type 1 Diabetes mellitus-why the β cells? Nat Rev Endocrinol 2016;12:263–73
32. Bindom SM, Lazartigues E. The sweeter side of ACE2: physiological evidence for a role in diabetes. Mol Cell Endocrinol 2009; 302: 193–202
33. Marchand L, Pecquet M, Luyton C. Type 1 Diabetes onset triggered by COVID-19. Acta Diabetol. 2020; 11:1–2.
34. Caruso P, Longo M, Esposito K, Maiorino MI. Type 1 Diabetes triggered by covid-19 pandemic: A potential outbreak. Diab Res and Clin Pract, 2020; 164:108219

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