Review

COVID-19 associated with diabetes and other noncommunicable diseases led to a global health crisis

Mark Thomaz Ugliara Barone [a,b,c,d,*], Belinda Ngongo [e], Simone Bega Harnik [f],
Lucas Xavier de Oliveira [a,b,g], Dániel Végh [a,h], Patrícia Vieira de Luca [c,i],
Hermelinda Cordeiro Pedrosa [d,j], Franco Giraudo [k,l], Roque Cardona-Hernandez [m],
Nayanjeet Chaudhury [n,o], Luiz Menna-Barreto [p]

[a] International Diabetes Federation (IDF), 166 Chaussee de La Hulpe B-1170 Brussels, Belgium
[b] ADJ Diabetes Brasil (ADJ), Rua Padre Antônio Tomás, 213, Zip Code 05003-010, Água Branca, São Paulo, SP, Brazil
[c] Fórum Intersetorial para Combate às DCNTs no Brasil (ForumDCNTs), Rua Padre Antônio Tomás, 213, Zip Code 05003-010, Água Branca, São Paulo, SP, Brazil
[d] Sociedade Brasileira de Diabetes (SBD), Rua Afonso Braz 579, Salas 72/74, Vila Nova Conceição, Zip Code 04511-011, São Paulo, SP, Brazil
[e] Pan African Women in Health (PAWH), P.O. Box 95535, Grant Park, 2051, South Africa
[f] Universidade de São Paulo (USP), Instituto de Matemática e Estatística, Departamento de Estatística, Rua do Matão 1010, Cidade Universitária, Zip Code 05508-090, São Paulo, SP, Brazil
[g] Liga de Enfermagem na Atenção ao Diabetes da Escola de Enfermagem da Universidade de São Paulo (LEAD-EE-USP), Av. Dr. Enéas Carvalho de Aguiar, 419, Zip Code 05403-000, Cerqueira César, São Paulo, SP, Brazil
[h] Semmelweis University, Faculty of Dentistry, Department of Prosthodontics, Budapest, Hungary
[i] Associação Brasileira de Hipercolesterolemia Familiar (AHF), Rua Machado Bittencourt 190, Vila Clementino, Zip Code 04044-000, São Paulo, Brazil
[j] Research Centre, Endocrinology Unit, Regional Taguatinga Hospital, Secretary of Health, Brasilia, Federal District, Brazil
[k] Institute Maternal and Child Research (IDIMI), School of Medicine, University of Chile, Santiago, Chile
[l] Juvenile Diabetes Foundation of Chile (FDJ), Santiago, Chile
[m] Hospital Sant Joan de Déu, Division of Pediatric Endocrinology, Barcelona, Spain
[n] Public Health Institute, Oakland, CA, 555 12th Street, Suite 215, Oakland, CA, 94607
[o] Ramaiah International Centre for Public Health Innovations, MS Ramaiah Nagar, MSRIT Post, Bangalore 560097, India
[p] Grupo Multidisciplinar de Desenvolvimento e Ritmos Biológicos (GMDRB), Escola de Artes, Ciências eHumanidades da Universidade de São Paulo (EACH-USP), Rua Arlindo Béttio, 1000 – Ermelino Matarazzo, São Paulo, SP 03828-000, Brazil

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ABSTRACT

COVID-19 has gravely threatened high-risk populations, such as people with diabetes and other noncommunicable diseases, leading to disproportionate hospitalizations and deaths worldwide. It is well documented from previous outbreaks that diabetes increases the risk for poor outcomes due to SARS infection. In the present review, we bring evidence that the country and global level health crisis caused by COVID-19 could have been avoided or extremely minimized if measures to protect high-risk populations were implemented timely. In addition to general lockdowns, testing, tracing, isolation and hygiene measures, other specific interventions for diabetes and comorbidities management were shown crucial to allow the continuation of care services during the pandemic. These interventions included: teleconsultation, digital remote education andmonitoring, e-prescriptions, medicine delivery options, mobile clinics, and home point-of-care tests. In conclusion, we recommend prompt actions to protect the most vulnerable groups, valuing knowledge and experiences from previous outbreaks and lessons learned during the COVID-19 pandemic, in order to shield communities, health systems and the global economy.

Contents

1.   Introduction

Diabetes Research and Clinical Practice, volume 166 [1], as well as other global journals, dedicated an issue in 2020 to COVID-19 articles. While most of them provided relevant data regarding epidemiological aspects, specificities and dynamics of the infection, vaccines and treatment development and/or adopted measures for transmission prevention, little was shared in terms of clusters of useful global lessons to protect populations with diabetes and other noncommunicable diseases (NCDs). Moreover, it is frustrating that most of the knowledge available from earlier Severe Acute Respiratory Syndrome (SARS) epidemics, especially about the higher risk

for severity and mortality on people with diabetes (PwD) and other NCDs [2,3], was ignored, and consequences on these populations were not timely and effectively predicted and prevented in most parts. One would expect that as soon as the cause of COVID-19 was identified as a new SARS virus (in this case, SARS-CoV-2), swift and specific measures would be adopted to protect higher risk populations and thus avoid a viral catastrophe on health systems. In this review, we bring together experiences from different countries highlighting strengths and weaknesses in their COVID-19 response. We emphasize the importance of leveraging previous and current

knowledge, especially those aimed to protect higher risk groups, such as individuals with diabetes. We recommend that lessons learned are not only safeguarded for future pandemics but rather should also be utilized to trigger adjustments in the ongoing global health crisis and its lasting effects.

1.1. Impact of COVID-19 on people with diabetes

Diabetes, cardiovascular diseases (CVD) and other NCDs were recognized as major risk factors to hospitalization, intensive care needs and death due to the novel 2019 coronavirus [4–13]. Data from different parts of the world, included both in the news and scientific reports, pointed out that the overall SARS-CoV-2 case-fatality rate of 2.3% was actually more than three times higher (7.3%) when diabetes was present [4]. In the official Brazilian Epidemiological Bulletin of August 8-15th, 2020, 31.49% of all accumulated COVID-19 deaths were associated with diabetes [14], similarly a rate of 29.8% was reported in Italy at the end of July [15], and even higher in a single hospital in Africa: 50% [16]. Authors of a recent meta-analysis found a 2.3-fold increase in the risk of severity and a 2.5-fold increase for mortality associated with COVID-19 in PwD [8]. Moreover, older age and comorbidities commonly associated with diabetes, such as obesity, hypertension, obstructive sleep apnea (OSA), renal, cerebrovascular and cardiovascular diseases, add on the risk for poor outcomes and death in the presence of SARS-CoV-2 [9,17–20]. In the Coronado study, involving 1367 hospitalized PwD in 53 French centers, in addition to old age, OSA, and the presence of other altered laboratory markers (increased AST and CRP, decreased eGFR and platelet count), microvascular and macrovascular diabetes complications were identified to be independently associated with high risk of intubation and early death on the 7th day of hospital admission (46.8 and 40.8%, respectively) [18].

It is crucial to highlight that besides preventing contagion, measures should focus on minimizing the risk of aggravation in case of infection. Different research groups reported that blood glucose levels (BG) were independently associated with odds of hospitalization, severity, and death of COVID-19 patients [6,17,21–24]. In addition to HbA1c levels [17,21], higher and more variable BG increased ICU admission and death rate [6,22,23]. Consequently, maintaining BG on target has become a mantra for PwD during the pandemic [16,25,26]. A retrospective study with 952 COVID-19 inpatients with type 2 diabetes (T2D), revealed that maintaining glycemic variability within 3.9 to 10.0 mmol/L (i.e. between 70 and 180 mg/dL) reduces the death rate by 10-fold [22]. Bode et al. emphasized that a high proportion of individuals with diabetes and hyperglycemia who were hospitalized (451 out of 1122 patients in 88 US hospitals) presented longer hospital stays respect those who did not have glycemic fluctuations (5.7 vs 4.3 days), and a higher mortality rate (28.8% vs 6.2%) [23]. Lamentably, these outcomes were not unexpected [24]. Researchers from China had already revealed in 2006 that a history of diabetes and raised plasma glucose levels were independent predictors of morbidity and mortality among patients with SARS [27]. Nevertheless, the development of promising vaccines and treatments were interrupted then

because of the absence of SARS re-emergence [28], despite the knowledge and predictions of ongoing transmission and escalation, as well as the need for early protection of the most at risk populations [29].

Therefore, the global health systems' crisis provoked by COVID-19 is, in reality, the consequence of inefficiencies in adopting early and effective measures to protect those with diabetes, other NCDs, and the elderly. With the absence of a vaccine or efficient antivirals against SARS-CoV-2, policies had to be swiftly implemented. Early measures seemed to be extremely limited in different parts of the world [16,30,31]. Among the countries that experienced high COVID-19 burden, Brazil was alerted that 34–54.5% of its adult population was at risk of severe COVID-19 [32]. IIn Mexico, confirmed associations between severe COVID-19 and premature death with NCDs prompted researchers to recommend early protection of these high-risk populations [10]. In the South and Central America (IDF SACA region), policies were put into place to protect individuals with diabetes only in 37% of the region, either through home delivery of medicines (16%) or provision of adequate medical supplies for 2–3 months upfront (21%) [30]. The declaration from the Brazilian Ministry of Health to provide people with NCDs sufficient medicine to cover a 3-month period was only effective to 21% of PwD supported by the public health system [33]. Because of the limited measures to protect these populations, 86% and 62.6% of the COVID-19 deaths were among people with comorbidities (most of them NCDs) in India and Brazil, respectively [14,34]. Meanwhile, the scenario was not better in Italy, where only 3.9% who died presented no comorbidities [15]. Thus, one could easily conclude that effective measures to protect individuals with comorbidities would have potentially reduced at least half hospitals' occupancy, total number of deaths, and burden of COVID-19 on the health systems, sparing some of its impact on the global economy.

1.2. Measures beyond physical distancing

In the case of diabetes, whilst general measures of physical distancing, wearing face masks, hand hygiene and stay-at-home were critical, additional strategies to protect these individuals' health and self-care routine needed to be planned. During the pandemic, glycemic changes were reported as a consequence of altered routine and difficulties to access health services and medicines [33,35,36]. Among individuals with diabetes, 59.4% and 78.4% experienced glycemic fluctuations in Brazil and in India, respectively [33,35]. Some of the potential causes included: increase in food consumption in 29.8% and 46.9% and decrease in physical activity in 59.5% and 69.1% PwD respectively in Brazil and India [33,35]. An increase in screen time was also reported in Brazil – 48.9% watching TV and 53.5% surfing the internet [33]. In addition, 38.4% of consultations or lab exams were postponed or cancelled in Brazil [33], while in India, 89.5% of PwD had their therapy disrupted by COVID-19 pandemic (which presented a significant positive correlation with age) [35]. In India, increase in mean HbA1c from 8.8% (73 mmol/mol) to 10% (86 mmol/mol) in individuals with type 1 diabetes (T1D), was attributed to, among other factors, "non availability of insulin/glucose strips during the lockdown period" [36]. IDF

SACA region countries reported shortages of medicines and supplies (68.4%), difficulties to access health services (57.9%) and even food and items of first necessity in this region [30]. Similar situation was reported in African and Western Pacific nations [7,37]. In the Philippines, only 10% of T1D individuals had no difficulties receiving their insulin, BG test strips and lancets [7]. In Jordan, children with T1D experienced a shortage of insulin and/or BG strips in 58.3% and 43.4% of the cases, respectively, during the lockdown [38]. Consequently, BG variability increased in 75.5% of them [38]. Therefore, stay-at-home guidance did not suffice and needed to be complemented with strategies to allow individuals with diabetes and other NCDs to access quality health services, medicines, and to ensure maintenance of a healthy lifestyle.

The potential impact on the medical supply chain was a global concern for PwD from the onset of the pandemic [39,40]. To ensure equitable access, some countries established policies to restrict over-stocking [41,42]. Furthermore, to prevent shortage, global entities, including PAHO [43], recommended PwD to stock medicines for at least 2 to 3 months. In addition to home delivery of medicines and/or provide them with adequate supply for 2–3 months, in some countries, health systems facilitated prescription refilling and allowed family members to collect drugs and supplies; all to reduce the need for PwD to leave their homes, protecting those with NCDs from additional exposure to the virus [16,30,33,38,41,44–46].

1.3.   Transitioning from In-person to telemedicine care

Telemedicine was one of the key strategies to enable individuals to continue receiving medical attention while staying safe at home [16,38,44,47–50]. Lack of other options and identified benefits of telemedicine led to its quick legal approval and reimbursement in several countries [33,45,46,49,51,52]. A variety of digital solutions were adopted in different places for diabetes care during the pandemic [41,53,54]. Some of them focused mainly on telephone calls. For PwD, teleconsultations allowed therapy adjustment to the new pandemic routine, preventing the predictable impact of changing mobility and other habits on glycemic control [33,41,50,55]. Telemonitoring allowed healthcare professionals (HCPs) and community health workers (CHW) to track potentially infected individuals, refer them to appropriate health services and monitor their isolation or the state of health of individuals with NCDs [56]. Other complementary digital health tools and strategies were quickly endorsed and implemented in different countries, including e-prescriptions and online education sessions to start new therapies or to teach self-care principles to newly diagnosed PwD [41,42,46,52,57]. However, building HCPs' capacity, knowledge, and confidence on the transition process from in-person to teleconsultations care was a key element for effective implementation [44].

1.4.   Communication as a strategy

If it is true that adjustments to the health systems were fundamental, commitment in communicating and educating appropriately PwD during the pandemic were key challenges to be addressed. WHO Regional Office for Europe stated, "specific advice should be made available nationally and locally for patients living with NCDs, their families, and their caregivers" [58]. Identifying that PwD watched more TV and surfed the internet for longer [33], Barone et al. suggested partnerships with media channels to promote healthy habits, exercise programs, and inform this population about ways to access telemedicine options – unfortunately availability does not always mean accessibility. Exercise, eating and other habits and routine were predicted and confirmed to suffer changes due to the pandemic [33]. Meanwhile, those who were able to exercise regularly and eat healthy experienced positive effects on BG even during the COVID-19 lockdowns [59]. Besides, knowing that sleep routine and duration are BG allies with potential to enhance the immune system [60,61], their inclusion as educational topics for PwD and caregivers is also recommended.

Delays in information and education to specific groups during the pandemic led to risky behaviors, such as reluctance to visit healthcare centers even during emergencies [62]. Consequently, different authors reported higher frequency and/or severity of diabetic ketoacidosis (DKA) in individuals with newly diagnosed T1D during the pandemic [62,63,64]. In Germany, the frequency of DKA at diagnosis during COVID-19 was significantly higher compared with the two previous years (44.7% in 2020, 24.5% in 2019, and 24.1% in 2018), as well as the incidence of severe DKA (19.4% in 2020, 13.9% in 2019, and 12.3% in 2018) [63]. In Italy, a 23%-reduction in new T1D cases was observed concomitantly with an increase in the proportion of severe DKA (44.3% in 2020 vs 36.1% in 2019) [64].

With respect to broad communication, though, one of the most remarkable paradoxes was how scientific organizations and the diabetes community in general reacted in the case of children and adolescents with diabetes. Whereas data from observational studies suggested that COVID-19 risk and prognosis in youths with diabetes seemed similar to their peers relatively milder than in adults (with or without diabetes) [64–66], many parents (and children) expressed concerns about the consequences of COVID-19 on their children with diabetes. This misinformation eventually led to unjustifiable discriminatory overprotective attitudes towards children and adolescents with diabetes after the relaxation of lockdown measures, specifically reopening of schools.

2.   Specific cases and strategies

Even though it does not seem that knowledge from previous SARS epidemics was efficiently used to timely prevent the global health crisis provoked by the COVID-19 pandemic, certain countries did a good job adopting specific measures in addition to lockdown, testing, tracing and isolating. Fig. 1 depicts case-fatality rate and cases of COVID-19 per million people from selected countries cited in this article, from 22 January to 5 September [67,68]. For instance, in the USA and Brazil, a high number of cases per million people was registered as well as a case-fatality rate around 3%. On the other hand, countries such as Italy and the United Kingdom faced the same level of cases per million with a much higher case-fatality rate (higher than 12%). In Slovenia, COVID-19
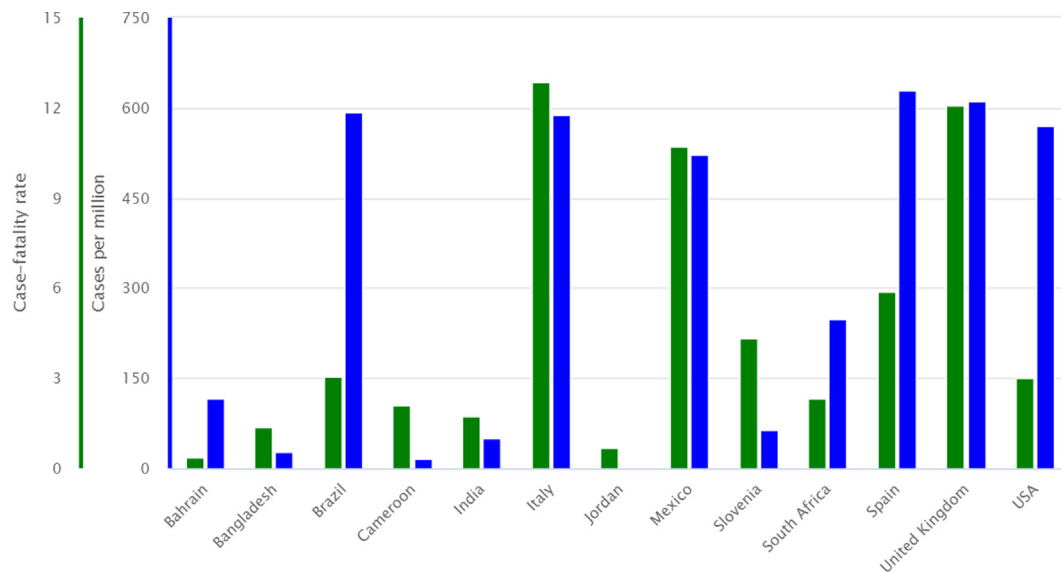
Fig. 1 – Case-fatality rate and cases per million of COVID-19 for selected countries (5th September 2020).

assumed a different pattern, with a smaller number of cases per million registered and a case-fatality rate of 4.3%. In Jordan, the cases per million were so low, 1.57, that the bar is not visible (Fig. 1).

Countries that adopted early general measures through making rapid health system adjustments, and specifically focused on supporting higher risk groups, such as elderly, PwD and other NCDs, experienced a less severe health crisis. While short-term outcomes of these investments resulted in more PwD with BG on recommended targets, lower hospital occupancy and mortality, a reduction of long-term chronic complications is expected, in addition to both short- and long-term burden on these countries' health systems.

Therefore, although there is no right or wrong strategy, we place emphasis on actions that were carefully thought, designed and implemented to avoid neglecting or leaving unassisted higher risk groups with diabetes and other NCDs, especially during lockdown and community transmission peaks. China and South Korea, regions where the outbreak had started and quickly spread, were among the countries that took advantage of their previous experience with the same family of viruses to implement broad measures and make systemic adjustments for diabetes care, publishing some of the first specific recommendations [7,26,54,69].

2.1. Development and adaptation of resources and channels

Diverse digital solutions including new applications, chatbots, traditional social media, and SMS messaging were adopted to disseminate information, educate PwD, trace individuals and monitor their health, support self-care and allow teleconsultations worldwide [16,38,44,47,52,56].

In Australia, Portugal and Italy partnerships and complementary action by the government with diabetes associations allowed rapid implementation and expansion of telehealth services to ensure continuity of diabetes care [42,46,50]. A clear lesson from these three countries, as well as from the

Federal University of Bahia (UFBA) in Brazil that partnered with the municipal Secretary of Health of Vitória da Conquista [56], is the need for proactive actions to reach PwD and HCPs providing timely guidance and information. The Portuguese Diabetes Association (APDP), which provided their HCPs with equipment and remote access to medical records, rearranged scheduled appointments and informed PwD by phone about available services and care pathways in case of emergency [46]. In Australia, each organization provided communication and updates to their respective members [42]. Countries such as Brazil missed a centrally orchestrated response by the Ministry of Health [31], setting up formal links with the civil and the scientific societies. At least a partnership comprising multiple scientific societies was developed to produce a guide for national public health networks, launched by the National Council of Health Secretariats in Brazil (CONASS, www.conass.org.br/guia).

For regions of Portugal that were not previously supported by APDP (outside the capital, Lisbon), a hotline was established with similar functions to the one launched by ADJ Diabetes Brasil. It allowed APDP and ADJ to provide telehealth diabetes services to individuals unable to access their routine health services [46]. Furthermore, APDP summarized recommendations from the Ministry of Health and international organizations and disseminated them through various channels including its website and social media outlets [46]. Similarly to what the Brazilian Diabetes Society (SBD – www.diabetes.org.br) and global organizations (as IDF, ADA, JDRF and KAP-WHO) did, the National Diabetes Services Scheme (NDSS – www.ndss.com.au) in Australia developed a rich and updated website with COVID-19/diabetes resources [42]. These measures represented a key move to stop infodemic and safeguard PwD from fake news. Otherwise, as in most countries, PwD lacked directions on how to access remote health services or when/how to seek a hospital.

Additional mass communication and education strategies were adopted worldwide. In China the application WeChat was used to share educational e-books and videos for PwD

[54]. In Australia webchats, podcasts and a guide were developed [42]. The United Kingdom wisely published a consensus document for treating PwD with COVID-19 and another for outpatients' appointment prioritization [49]. A guide for HCPs was also made available in Bangladesh [70]. Online support groups were reported in Scotland and Brazil [57]. Remote diabetes courses and webinars for lay people and HCPs were launched or expanded in many countries, including Australia, Brazil, Chile, Ecuador, Portugal, UK and Uruguay, just to name a few [37,42,46,57].

2.2. Additional innovative approaches

Even though telemedicine was the main resort to diabetes care during lockdown and "stay at home" periods, the great majority of worldwide populations still exhibit limited digital literacy and/or access to the internet [16,48,51]. An alternative developed in Bahrain – in addition to the prompt switch of the endocrinology outpatient department at the King Hamad University Hospital to telemedicine on March 16th – was the establishment of innovative remote clinics to bring HCPs, using hospital's home healthcare vehicles, to PwD's doorstep [45]. For this same reason, despite the strong preference for video-consultations, in many cases, including in the United States, some teleconsultations were limited to telephone calls, removing part of the digital literacy barriers [48,51,56]. These measures, among others discussed in this article, align with PAHO's recommendation of "actively ensuring that vulnerable populations have equitable access to care" [44].

In Koper, Slovenia, telemedicine was associated with a postal HbA1c test kit [53]. Not only were the satisfaction rates of measuring HbA1c this way above 90%, but it also represented an effective alternative for healthcare teams to monitor PwD, especially those who do not use continuous glucose monitoring or uploadable glucometers. This strategy to obtain HbA1c results was also encouraged in the United Kingdom [49], where a group expanded postal tactics to urinalysis dipsticks to continue measuring albumin-to-creatinine ratio of PwD supported [57].

3. Lessons Learned: New Normal and Barriers

Telemedicine and other digital strategies were among the most successful strategies during the pandemic and are seen as permanent [16,45–47,49,71]. They allowed continuity of diabetes care in a safe and flexible manner [53,55], reducing no-show rates − 4% only in Bahrain [45] – and alleviating part of the pressure by optimizing health systems' resources. With restriction to in-person consultations, PwD and other NCDs in a certain level benefited from having easier access to their healthcare teams, availability of flexible time schedules, access to online educational materials, while avoiding barriers as distance, time and inflexible time schedule for consultations. As an investment in adherence, we encourage governments and health systems to maintain telehealth services, online prescriptions refill and upfront distribution of supplies for 2–3 months and/or home delivery.

3.1. Social inequalities hinder effectiveness of measures

Despite digitalization of health services, socioeconomic inequalities constituted an additional barrier when planning appropriate protective measures. Epidemiologists and social scientists alerted on constraints faced by underserved populations to adhere to hygiene, stay at home and physical distance measures [16]. This particularly affected populations like slum dwellers, where large families are crammed in small living spaces in vulnerable areas, and where people have no option but to commute daily to work. These additional challenges were clearly reported in studies in LMIC. In some African and Latin American countries, food insecurity and lack of financial health protection was a reality for PwD [30,37]. In Brazil, individuals depending exclusively on the public health system were less compliant with the stay-at-home recommendations and often experienced an increase in BG [31,33]. In India, only 47.4% had a glucometer at home, 62.5% did not buy all the medicine they needed due to financial reasons, and only 29.8% had access to teleconsultation during the pandemic [35]. In Africa, a similar scenario was reported as many PwD were unable to buy their medicines, rationed insulin, skipped oral drugs and/or were unable to self-monitor their BG [16].

BG worsening was reported in Brazil, India, China and African countries [16,31,33,35,36], while the opposite situation was observed in T1D groups in high income countries (HIC). With access to advanced technology, treatment, specialized services and HCPs used to digital health tools, PwD in HIC maintained or even improved their BG levels during the pandemic [59,61,72,73,74]. In comparison with the pre-pandemic period, time in range of individuals with T1D using glucose sensors increased from 57.8% to 62.5%, in Spain [73], and from 55.8% to 58.2%, in Italy [61]. However, negative consequences of inequalities were also present in HIC [17,51]. Low access and limited digital literacy led to reduction in teleconsultations in the United States [51], and increased mortality of socioeconomically deprived PwD in England [17]. Therefore, socioeconomic inequalities must be considered and social determinants of health need to be addressed concomitantly with health-oriented measures, otherwise they may impede commitment with protective measures.

3.2. Health systems preparedness

The pandemic revealed, again, the importance of investing in health systems building blocks including strengthening the healthcare workforce as well as policies for universal health coverage (UHC) and primary healthcare (PHC). Wang et al. alerted about the gap in diabetes knowledge among frontline emergency HCPs [54]. When a significant proportion of hospital beds are occupied by PwD and acknowledging that a deterioration in their BG would increase mortality risk significantly along with worsening diabetes complications and comorbidities, skills of HCPs would be expected to include monitoring BG and treating hyperglycemia of inpatients with COVID-19 [24]. Though, we suspect that this was not always the case in hospitals in different countries. Concerned with this risk, Diabetes UK produced and shared a

front door guidance on COVID:diabetes for hospitals [49]. SBD, in Brazil, also produced a guide (www.diabetes.org.br/publico/images/Emkt_SBD_Diabetes_na_Era_COVID-19_Horizontal.pdf), and Bangladeshi organizations, in partnership with IDF, produced an extensive and detailed resource [70].

Inevitably, pandemic preparedness depends enormously on the state of the healthcare infrastructure. Resilient systems to prevent and treat diabetes and other NCDs, lead to lower NCDs prevalence and better metabolic control, resulting in reduced pandemic morbidity and mortality [75]. We understand that among the priority components for a timely effective response, countries and their health systems must have a well-structured UHC with a robust interconnected medical data-system, and linked to a solid supply-chain. Additionally, partnerships between the public, private and not-for-profit health organizations, civil society, and other sectors certainly speed up the adaptation of the health systems [33,34,42,44,46,50].

Knowledge from preceding and current pandemics and epidemics must be readily available for governments and decision makers to prepare and react in an effective and timely manner to protect the population and reduce the burden on the health systems and their economies. COVID-19 was seriously underestimated. The world believed that with all medical advances, we would conquer it in a short time. Instead, the new coronavirus decimated a significant proportion of the population, especially the ones with diabetes and other NCDs. Therefore, knowledge from prior pandemics and epidemics should be considered valuable assets to identify and support highly susceptible groups and to quickly design and implement measures for protecting them. We hope that in future pandemics, no matter the composition of higher risk groups – children, elderly, PwD, Europeans, Andeans, or others – we are better prepared and more alert to prevent health systems' collapse and avert millions of deaths by protecting them early.

The limitation of the present review lies in the fact that it is neither a meta-analysis nor a systematic review, but a gathering of multi-country efforts intended to raise meaningful evidence to understand weaknesses and strengthsof measures to protect PwD during the COVID-19 pandemic and, thus allow countries worldwide to improve current and future responses.

4. Conclusion

The COVID-19 pandemic has taught important lessons and is reminding us of prioritizing vulnerable populations. Unfortunately, millions with diabetes and other NCDs have died due to lack of preparedness or inadequate responses. General measures, such as hygiene, physical distance and face masks, did not suffice to protect PwD. Telemedicine, including tele-consultation and other digital health tools, was among the most effective strategies to keep individuals safe while maintaining their chronic condition care. Partnerships between public, private and not-for-profit, including scientific and civil society, have shown to add key alternatives to assist the underserved and improve care. Among the developed tactics, we would highlight partnerships with media channels, development of digital educational materials and data platforms, online medicine refills, distribution of medical supplies for an extended period, launching of hotlines, production of easily usable health protocols and courses, postable point-of-care tests, and adapted home visits or delivery of medicines. Meanwhile, we identified that uncoordinated decentralized plans, lack of infrastructure and social inequities constituted barriers for the success of governments' and health systems' responses.

We hope that this time the world will learn from this pandemic. The potential return of previous families of viruses should not be underestimated, and accumulated knowledge must be promptly used to identify and support the most vulnerable populations, such as people with diabetes and other NCDs, the elderly or other groups. In conclusion, only through a globally coordinated action, we will be able to prevent extreme mortality rates, avoid dire global health systems consequences and economic collapse that several countries faced during the COVID-19 pandemic.

Ethics approval and consent to participate

Not applicable.

Consent for publication

All authors are fully aware and consent in publishing the present manuscript.

Availability of data and materials

Not applicable.

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.

Authors' contributions

Mark Thomaz Ugliara Barone led the designing of this article. All authors contributed equally in preparing, writing and reviewing it.

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