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.

Diabetes & Metabolic Syndrome: Clinical Research & Reviews 15 (2021) 447–454

Contents lists available at ScienceDirect

Diabetes & Metabolic Syndrome: Clinical Research & Reviews

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

The association between COVID-19 and type 1 diabetes mellitus: A systematic review

Mahmoud Nassar, MD, MSc, MHA, MPA. [a, *], Nso Nso, MD/MPH [a], Bahaaeldin Baraka, MD, MRCP [b], Mostafa Alfishawy, MD [c], Mahmoud Mohamed, MD [d], Akwe Nyabera, MD [a], Issac Sachmechi, MD [e]

[a] Department of Medicine, Icahn School of Medicine at Mount Sinai/NYC H&H Queens, NY, USA
[b] Oncology Department, Southend University Hospital, Mid and South Essex NHS Foundation Trust, ESSEX, UK
[c] Infectious Diseases Consultants and Academic Researchers of Egypt IDCARE, Cairo, Egypt
[d] Department of Medicine, Division of Nephrology, University of Tennessee Health Science Center, USA
[e] Division of Endocrinology, Department of Medicine, Mount Sinai Services, Queens Hospital, Center, NY, USA

ARTICLE INFO

Article history:
Received 25 December 2020
Received in revised form
2 February 2021
Accepted 4 February 2021

Keywords:
COVID-19
T1DM
Diabetes mellitus
New onset

ABSTRACT

Background: /Aim: Various reports of the occurrence of type 1 diabetes mellitus (T1DM) in patients with COVID-19 have been published, denoting an association between both diseases. Therefore, we conducted this systematic review to summarize the prevalence of T1DM in COVID-19 patients and to identify the clinical presentations and outcomes in this patient population.

Materials and methods: Up to 10/27/2020, Medline, Embase, cochrane and google scholar databases were searched for original studies investigating the association between COVID-19 and T1DM. A manual search was conducted to identify missing studies. The quality of included studies was analyzed by the National Institute of Health (NIH) risk of bias tool. Outcomes included length of hospital stay, hospitalization, intensive care unit (ICU) admission, diabetic ketoacidosis (DKA), severe hypoglycemia, and death.

Results: Fifteen studies were included in the qualitative analysis. Included studies reported data of both adult and pediatric patients. The prevalence of T1DM in COVID-19 patients ranged from 0.15% to 28.98%, while the rate of COVID-19 in patients with T1DM ranged from 0% to 16.67%. Dry cough, nausea, vomiting, fever and elevated blood glucose levels were the most commonly reported presentations. The investigated outcomes varied widely among studied populations.

Conclusions: The prevalence of T1DM in patients with COVID-19 ranged from 0.15% to 28.98%. The most common presentation of COVID-19 in patients with T1DM included fever, dry cough, nausea and vomiting, elevated blood glucose and diabetic ketoacidosis. The outcomes of COVID-19 in terms of length of hospital stay, hospitalization, ICU admission, DKA rate, and severe hypoglycemia were reported variably in included studies. Due to the heterogeneous study populations and the presence of many limitations, more studies are still warranted to reach a definitive conclusion.

1. Introduction

On March 11, 2020, the World Health Organization (WHO) recognized the emerging COVID-19 (CoronaVirus Disease-2019) as pandemic after recording over 118,000 cases globally in 114 countries [1]. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is the strain of coronavirus that causes COVID-19. The RNA virus belongs to the previously merging corona family featured with respiratory manifestations with high case fatality [2,3]. Virus acquisition can occur either by contact directly with infected

* Corresponding author. Department of Medicine, Ilcahn School of Medicine at Mount Sinai/ NYC H&H Queens Hospital Center, 82-68 164th Street Jamaica, New York, 11432, NY, USA.
E-mail addresses: Mahmoud.Nassar@MountSinai.org, Nassar@aucegypt.edu (M. Nassar), mcviali@yahoo.co.uk (N. Nso), bahaabaraka@gmail.com (B. Baraka), malfishawy@kasralainy.edu.eg (M. Alfishawy), Mmohame3@uthsc.edu (M. Mohamed), anyabera1@gmail.com (A. Nyabera), SACHMECI@nychhc.org (I. Sachmechi).

https://doi.org/10.1016/j.dsx.2021.02.009
1871-4021/

subjects or indirectly with contaminated objects within the environment while asymptomatic patients can spread the disease [4,5].

Patients with COVID-19 experience a variety of clinical presentations ranging from no symptoms or mild illness to critical illness with multi-organ failure even death [6,7]. Mortality rate of COVID-19 ranges from 0.7% to 10.8% [8]. Survival decreases, and more complications tend to develop in advanced age populations and patients with underlying comorbidities [9]. This has raised concerns about those suffering chronic conditions like Type 1 Diabetes Mellitus (T1DM) [10–12].

Reports prove no increase in the risk of infection with COVID-19 among children with T1DM and adolescents [13]. Besides, no present evidence is suggesting higher mortality rates in T1DM children in comparison with their healthy peers. However, poor outcomes and more deaths are recorded in diabetic adults after COVID-19 infection [12].

We did not find robust information discussing the consequences and the direct correlation between Covid-19 and T1DM [12]. On the other hand, reports are showing that COVID-19 indirectly carries risks for T1DM patients on many levels; in some countries, it may hinder obtaining adequate health services. The interrupted supply of drugs, technology, and care for T1DM patients can result in poor glycemic control and, subsequently, more complications [13]. It also delays the proper response to emergency situations since a significant reduction is reported in emergency department access mainly because of fear of infection [14]. Also, the pandemic is accused of aggravating adaptive psychological difficulties among T1DM children [15]. Therefore, we conducted this systematic review to summarize the prevalence, clinical findings, and outcomes of COVID-19 in patients with T1DM, based on the findings of available evidence.

2. Materials and Methods

2.1. Search strategy and study selection

The study process was conducted following the accepted methodology recommendations of the PRISMA checklist for systematic review and meta-analysis, where registration of the protocol is not mandated [16]. A systematic electronic database search was conducted for relevant studies published from inception and till 10/27/2020 in 4 databases including Embase, Medline, Cochrane and Google scholar databases using keywords, medical subject (MeSH) terms and publication types based on the PICO framework (participants, comparison, intervention, and outcomes). The following search terms were used according to each database: (COVID-19 OR SARS-CoV-2 OR nCoV-2) AND (T1DM OR “type 1 DM” OR “type 1 diabetes”). The inclusion criteria were as follows (1) all original studies (i.e., cohort, cross-sectional, and case-control studies): that report the incidence of T1DM in COVID-19 patients or vice versa, (2) commentaries and case series that included more than 10 patients, and (3) studies that reported the clinical characteristics and outcomes of patients with both T1DM and COVID-19. On the other hand, the exclusion criteria included the following: (1) non-original reports (i.e., reviews, letters to editors and commentaries that did not include original patients’ data), (2) case reports and case series including less than 10 patients, (3) unavailable full-texts, (4) unextractable or irrelevant data (such as the psychological impact of COVID-19 pandemic on patients with T1DM without infection), (5) articles that were not published in English, (6) duplicated records, (7) animal studies, and (8) overlapped data.

The primary outcome was to determine the number of COVID-19 patients who had either known or newly diagnosed T1DM and vice versa. The secondary outcomes included the clinical characteristics, radiographic findings, and outcomes/complications (i.e., hospitalization rate, ICU admission rate, length of hospital stay, rate of diabetic ketoacidosis (DKA), and death) in patients with both COVID-19 and T1DM.

We further did a manual search of references in our included papers to avoid missing relevant studies. We included all original studies that reported both COVID-19 and T1DM. The title and abstract screening were performed by four independent reviewers. Then, three independent reviewers performed a full-text screening to ensure the inclusion of relevant papers in our systematic review. Any disagreement was resolved by discussion and referring to the senior author when necessary.

2.2. Data extraction

Two authors developed the data extraction sheet using the Microsoft Excel software. Data extraction was performed by three independent reviewers using the excel sheet. The fourth independent reviewer performed data checking to ensure the extracted data accuracy. All the disagreements and discrepancies were resolved by discussion and consultation with the senior author when necessary.

2.3. Quality assessment

Three independent reviewers evaluated the risk of bias in the included studies. The National Institute of Health (NIH) risk of bias assessment tool was used to assess the quality of included studies [17]. Three different tools were used: one for cohort and cross-sectional studies (14 questions/items), one for case-control studies (12 questions/items), and one for case series (9 questions/items). Any discrepancy between the reviewers was solved through discussion.

2.4. Statistical analysis

Due to the scarcity of reported outcome data in included studies with the wide variations in the studied populations, the conductance of a meta-analysis was inapplicable.

3. Results

3.1. Search results

We identified 893 records after excluding 103 duplicates using the Endnote X9 software. Title and abstract screening resulted in 40 records for further full-text screening. Two papers were added after performing manual search trials. Finally, we included fifteen studies in this systematic review after excluding 27 papers from the full-text screening phase (Fig. 1).

3.2. Study characteristics and quality of the included studies

The baseline characteristics of included studies are summarized in Table 1. Fifteen studies were finally included: Eight studies are retrospective cohort studies, three are cross-sectional studies [18–24], two are retrospective case-control studies [25,26], one is retrospective case-series [27], and one was a commentary with no clear report of a study design, but the study included original data [28]. The studied populations were patients with COVID-19 alone in two studies [22,27], patients with T1DM alone in five studies [14,21,23,24,28], patients with both COVID-19 and T1DM in five studies [18–20,29,30], and patients with either COVID-19 and T1DM (case group) and patients with T1DM alone or with COVID-19-like disease (control group) in two studies [25,26]. The sample

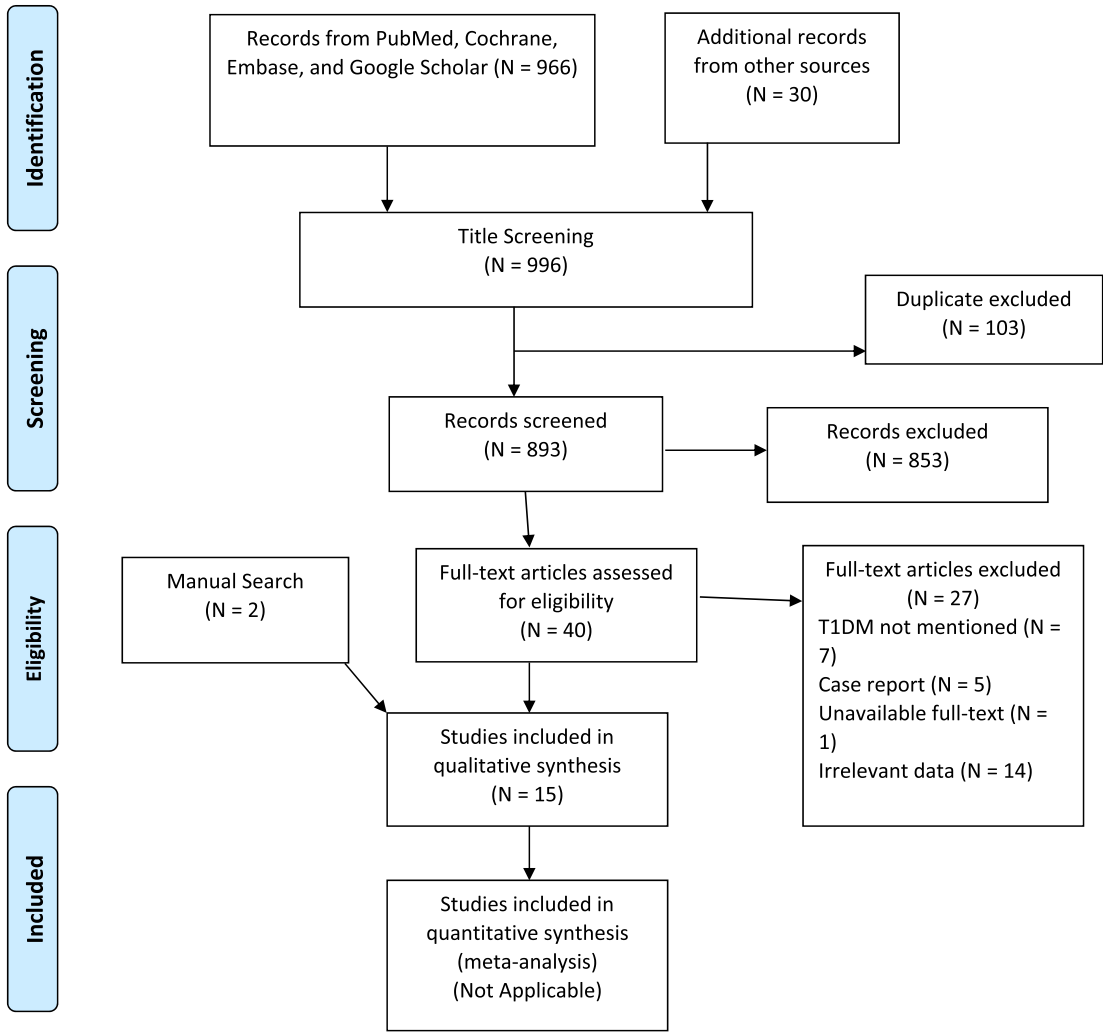

Fig. 1. PRISMA flow diagram of the screening process of this systematic review.

size of included studies ranged from 32 participants [18] to 264,390 participants [21]. The age of included patients was variable, ranging from pediatric age group to adults and elderly patients. Meanwhile, male patients were present in 39.10%–68.0% of studied populations [24,25].

3.3. Prevalence of COVID-19 in T1DM and vice versa

None of the included studies was designed primarily to determine the prevalence of COVID-19 in patients with known T1DM or to determine the prevalence of new-onset T1DM in patients with confirmed SARS-CoV-2 infection. However, the rate of SARS-CoV-2 infection was reported in six studies investigating patients with T1DM [14,23,24,28,29,44], with a prevalence rate ranging from 0% [28] to as high as 16.67% (5/30 participants) [24]. Meanwhile, in patients diagnosed with confirmed COVID-19, the rate of T1DM (regardless of being newly-diagnosed or with known diabetes) ranged from 0.15% (1/658 participants) [22] to 28.98% (20/69 participants) [27].

3.4. Clinical presentation of patients with T1DM and COVID-19

Four studies reported the clinical findings of COVID-19 in patients with T1DM [18,25,27,30]. Nausea and vomiting were the most common presentation of COVID-19, accounting for 71.40% (5/7) of patients in the study of Al Hayek et al. [18] Dry cough was the most common presentation (51%; 58/113) in the study of O'Malley et al. [30] Fever was the most common presentation (89.9%; 62/69) in the study of Yang et al. [27] Finally, elevated blood glucose level was the most common presentation both in the case group (COVID-19 and T1DM; 48.5%) and in the control group (COVID-19-like disease and T1DM; 51.60%) in the study of Ebekozien et al. [25] The radiographic findings of patients with both COVID-19 and T1DM were not reported in any of the included studies.

3.5. Clinical outcomes and complications

The outcomes or endpoints, such as death, hospitalization rate, intensive care unit (ICU) admission rate, DKA, and severe hypoglycemia, were reported in the majority of included studies. The rate of ICU admission ranged from 13.3% [25] to 25.90% [28]. Meanwhile, the rate of intubation alone (not as a composite outcome) was reported in only one study with a rate of 5.3% (6/113 patients) [30]. Meanwhile, the rate of DKA was reported in four studies [24,25,28,30], ranging from 24.0% [30] to 51.7% [28]. Severe hypoglycemia was reported as an outcome in only two studies [25,30], with a rate of 5.31% and 3.0%, respectively. The rate of COVID-19-related death or mortality was 0% [18], 1.50% [19], 3.0%

Table 1
Baseline characteristics of included studies of patients with T1DM and COVID-19 (N = 15).

Author/YOP/ Country	Study Design	Population	Sample size	Age		Sex (male)	Outcome (Study group)			Outcome (Control group)			Prevalence of T1DM		Prevalence of COVID-19	Quality rating (NIH)
				mean	SD	N (%)	N	%	type	N	%	type	N (%)	Type	N (%)	
Barron/ 2020/UK [31]	Population-based	COVID-19-related death cases	23,698	all age groups		14,579 (61.5%)	364	1.50%	COVID-19-related death in T1DM cases				23,698 (100%)	NS	NR	Poor
Vamvini/ 2020/USA [32]	Commentary-Retrospective case-control study	Case (hospitalized patients with T1DM and COVID-19) vs. control (T1DM alone)	35	case (51.8%) vs. control (52.3)	case (13.4) vs. control (12.9)	17 (48.57%)	1	14.28%	DKA	2	7.14%	DKA	NA	NA	NA	Poor
							2	28.50%	CAD/CVD	8	28.50%	CAD/CVD				
							10.6 (8.2)		Length of hospital stay	7.3 (6.6)		Length of hospital stay				
							2	28.50%	composite outcome (ICU, intubation, or death)	4	14.30%	composite outcome (ICU, intubation, or death)				
Bhatti/2020/ UAE [33]	Cross-sectional study	COVID-19 and DM	103	45	12.5	69 (67%)							103 (100%)	NS	3 (2.90%)	Poor
Al Hayek/ 2020/ Saudi Arabia [34]	Retrospective study	Patients with COVID-19 and T1DM	32	all age groups		14 (43.80%)	7	21.90%	hospitalization				32 (100%)	Known T1DM	32 (100%)	Poor
							0	0.00%	death							
Di Dalmazi/ 2020/Italy [35]	Retrospective cohort study	Patients with T1DM	130	all age groups		71 (54.60%)							130 (100%)	Known T1DM	1 (0.77%)	Poor
O'Malley/ 2020/USA \[30]	Multicenter cross-sectional study	Patients with T1DM and COVID-19	113	39.9	16.4	55 (48.67%)	58	51.32%	hospitalization				111 (98.33%)	Known T1DM	113 (100%)	Poor
							5	4.00%	death				2 (1.77%)	Newly diagnosed T1DM		
							27	24.00%	DKA							
							6	5.31%	intubation							
							6	5.31%	Severe hypoglycemia							
Li/2020/ China [22]	Retrospective cohort study	Hospitalized patients with COVID-19	658			297 (45.14%)							1 (0.15%)	NS	658 (100%)	Poor
Rabbone/ 2020/Italy [36]	Cross-sectional study	Patients with T1DM	160	0-14#									160 (100%)	NS	8 (5%)	Poor
Pla/2020/ Spain [37]	Retrospective cohort study	Patients with T1DM	50	43.4	15.6	23 (46%)							50 (100%)	NS	1 (2%)	Poor
Yang/2020/ China [38]	Retrospective case series	Hospitalized patients with COVID-19	69	61[a]	52-67[a]	34 (49.30%)							20 (28.98%)	COVID-19-related Diabetes	69 (100%)	Poor
Unsworth/ 2020/UK [39]	Commentary-Multicenter regional study	Patients with T1DM	33	1.9–16.8#		22 (68%)	12	36.00%	Severe DKA				30 (90.10%)	Newly diagnosed T1DM	5 (16.67%)	Poor
Cariou/2020/ French [40]	Multicenter observational study	Diabetic patients hospitalized for COVID-19	1317	69.8	13	855 (64.90%)							39 (3%)	NS	1317 (100%)	Poor
Atlas/2020/ Australia [41]	NR	Patients with T1DM	58			32 (55.20%)	15	25.90%	ICU admission				58 (100%)	NS	0 (0%)	Poor

							30	51.70%	DKA								
Holman/ 2020/UK [42]	Population-based cohort study	Patients with T1DM	264,390	all age group		149,680 (56.60%)	432	0.16%	COVID-19 related death				264,390 (100%)	NS	NS	Poor
Ebekozien/ 2020/USA [43]	Multicenter case-control study	Case (T1DM and COVID-19) vs. control (COVID-19-like and T1DM)	64	20.9	14.84	25 (39.10%)	10	30.30%	ICU admission	4	13.30%	ICU admission	NA	NS	NA	Poor
							9	27.20%	Hospitalization	2	6.70%	Hospitalization				
							1	3.00%	Death	1	3.30%	Death				
							15	45.50%	DKA	4	13.30%	DKA				
							1	3.00%	Severe hypoglycemia	2	6.70%	Severe hypoglycemia				

[a] Median and Interquartile range; #: Range; NR: Not Reported; NS: Not Specified; NA: Not Applicable (case-control study); DM: Diabetes Mellitus; T1DM: Type 1 Diabetes Mellitus; ICU: Intensive Care Unit; DKA: Diabetic Ketoacidosis; NIH: National Institute of Health Quality Assessment Tool.

[25], and 4.0% in studied populations of COVID-19 and T1DM [30].

3.6. Risk of bias of included studies

All of the fifteen included studies had a high risk of bias (low quality) based on the assessment through the NIH tool (Table 1).

4. Discussion

4.1. The association between T1DM and COVID-19

Although many studies, including systematic reviews and meta-analyses, that investigated the association between COVID-19 and T1DM have been published, this is the first comprehensive review to systematically summarize the association between both conditions, the most common presentation, and the clinical outcomes of patients with COVID-19 and T1DM. In our review, we included a total of 15 studies (8 retrospective cohort studies, 3 cross-sectional studies, 2 retrospective case-control studies, 1 retrospective case series, and 1 study of non-specified design). The prevalence of T1DM (known, newly-diagnosed, and non-specified) in patients with SARS-CoV-2 infection was reported in three studies. In the study of Li et al. [22], the prevalence of T1DM was 0.15% (1/658), while it was 3.0% (39/1317) in the study of Cariou et al. [20] Yang et al. [27] conducted a study among hospitalized patients with COVID-19, and they found that COVID-related T1DM (fasting plasma glucose of 7 or more mmol/L 2 months during hospitalization without a previous diagnosis of diabetes) occurred in 28.98% (20/69) of patients. This difference could be attributed to the differences in studied populations, the timing of conduction of the study (during the early pandemic vs. during the late pandemic). Inconsistently, Kumar et al. [45] conducted a systematic review and meta-analysis of case-control studies to investigate the prevalence of DM in patients with confirmed COVID-19 diagnosis. The authors included 33 studies in their final meta-analysis, which revealed that the pooled prevalence of DM in patients with COVID-19 was 9.8% (95% confidence interval (CI) = 8.7%–10.9%) after adjusting for the encountered heterogeneity. This finding is different from ours, but this could be attributed to the fact that these authors investigated the prevalence of DM, overall, and not just T1DM. And, the low rate of T1DM among COVID-19 patients in our study could be explained by the fact that T1DM is far less common compared to type 2 DM (T2DM), which was reported in the majority of analyzed studies in the review of Kumar et al. [45] Another possible factor is that some of these studies may have been conducted in areas where COVID-19 was highly prevalent, while it was less prevalent in other countries.

Moreover, it is hypothesized that SARS-CoV-2 might itself cause diabetes. This has been observed in the previous SARS-CoV-1 infection [46]. Therefore, the association between COVID-19 and new-onset diabetes still warrants further investigation in both adults and young children. In this context, we also aimed to investigate whether COVID-19 increased the incidence of newly-diagnosed T1DM; however, relevant data were only reported in two studies. Ebekozien et al. [25] included patients with COVID-19 and T1DM; among them, 15.6% (5/33) had new-onset diabetes. This rate was higher than the study of O'Malley et al. [30], with a prevalence rate of 1.77% (2/113). On the other hand, Unsworth et al. [24] reported a prevalence rate of new-onset diabetes of 90.1% (30/33) among 33 diabetic patients, of whom only 5 were diagnosed of COVID-19. This substantial difference could be explained by the minimal number of included participants in each study, which would result in the over- or under-estimation of the real burden of COVID-19 among patients with T1DM.

4.2. The presentation of COVID-19 in patients with T1DM

Four studies reported the most common presenting symptoms of COVID-19 in patients with both T1DM and COVID-19. In the study of Al Hayek et al. [18], nausea and vomiting, as well as DKA, were the most common presenting symptoms (5/7, 71.40%). In the study of O'Malley et al. [30], dry cough was the most common presentation (58/113, 51.0%) followed by fever or elevated body temperature-not specified- (56/113, 50.0%). Meanwhile, in the study of Yang et al. [27], fever was the most common presenting symptom (62/69, 89.90%) followed by cough (45/69, 65.2%). Furthermore, Ebekozien et al. [25] compared the presentation between cases (COVID-19 and T1DM) and controls (COVID-19-like disease and T1DM), and they found that high blood glucose levels, fever, and dry cough were the most common presenting symptoms in both the case and control groups; however, the presentation of these symptoms was slightly higher in the case group. Based on the scarcity of relevant data, no conclusions can be drawn regarding the presentation of COVID-19 in patients with T1DM due to the variation in the studied population (the incidence of these symptoms differ from hospitalized patients to community-based or population-based studies).

4.3. The clinical outcomes and complications in patients with T1DM and COVID-19

Death due to COVID-19 was reported as a single outcome or a composite outcome in some of the included studies. For instance, Barron et al. [19] reported that 1.50% (364/23,698 patients) of patients with T1DM died from COVID-19. Noteworthy, the reported rate of 1.50% does not reflect those with both T1DM and COVID-19 but rather describe the death rate due to COVID-19 among the overall studied population. Meanwhile, Vamvini et al. [26] studies cases with COVID-19 and T1DM and a control group T1DM patients alone. The authors reported that composite outcome (ICU admission and/or intubation and/or death) was dramatically higher in the case group, with a rate of 28.50% (2/7) compared to the 14.30% (4/28) in the control group. However, there was no statistically significant difference between both groups, and this could be attributed to the very small sample size. Noteworthy, Al Hayek et al. [18] found no mortality cases in patients with T1DM and COVID-19. Inconsistently, the mortality rate was lower in the study of O'Malley et al. [30], who reported a rate of 4.0% (5/113). On the other hand, the rate of COVID-19-related death was very low in the study of Holman et al. [21], who reported a rate of 0.16% (432/264,390). Furthermore, in the study of Ebekozien et al. [25], it was noted that the mortality rate was slightly lower in the case group (COVID-19 and T1DM, 3%), compared to the control group (COVID-19-like disease and T1DM, 3.3%). Of note, Yang et al. [27] found that COVID-19-related T1DM was significantly associated with a higher mortality rate compared to peers (P = 0.0019). On the other hand, the study of Cariou et al. [20] reported that the risk of death was lower in patients with T1DM (OR = 0.44; 95% CI: 0.11–1.86). However, this difference did not reach statistical significance. This wide variation in the rate of COVID-19-related deaths in the studied populations, as well as the differences in the risk of death in T1DM, may be attributed to many factors. For instance, the clinical heterogeneity in studied populations (hospitalized patients vs. community-based cases; adults vs. children; the presence of comorbidities vs. absence of comorbidities) could substantially impact the interpretation of these findings. Also, the burden and/or the prevalence of COVID-19 in different regions of the world is not the same, and the exact reason for this variation is not yet clearly understood, and this could possibly account for the differences in our findings.

Diabetic ketoacidosis was a prevalent outcome in patients with COVID-19 and T1DM. The rate of DKA was lowest in the study of Vamvini et al. [26], with a rate of 14.28% (1/7); however, this rate was higher than that observed in controls (without COVID-19, 7.14%; 2/28). Other studies reported higher rates of DKA in patients with COVID-19 and T1DM, where O'Malley et al. [30], reported a rate of 24.0% (27/113), Unsworth et al. [24] reported a rate of 36.0% (12/33), and Atlas et al. [28] reported a rate of 51.7% (30/58). Noteworthy, in the study of Ebekozien et al. [25], it was noted that the rate of DKA in patients with COVID-19 (case group) was three folds that of patients without COVID-19 (control group) (45.5% vs. 13.3%), respectively.

Length of hospital stay was only reported in one study, where patients with both COVID-19 and T1DM had higher mean hospital stay compared to patients with T1DM alone (10.6 vs. 7.3 days); however, this difference did not reach statistical significance. The rate of hospitalization was only reported in two studies since many studied included hospitalized patients in the first place. The hospitalization rates ranged from 27.2% in the study of Ebekozien et al. [25] to 51.32% in the study of O'Malley et al. [30] Among patients with T1DM and COVID-19, 25.90% and 30.3% of patients were admitted to the ICU, as reported in two studies [25,28]. Meanwhile, severe hypoglycemia was reported in only two studies, with a relatively low occurrence rate of 3.0% in the study of Ebekozien et al. [25] and 5.31% in the study of O'Malley et al. [30].

The subacute injury of the islet of Langerhans of the pancreas caused by a viral infection has been widely reported in T1DM, which is an autoimmune condition highlighted by a long-term loss of pancreatic beta cells. Meanwhile, the acute injury of the islets has been minimally reported in the literature. However, it has been previously reported that viruses were isolated from pancreatic islets with serological evidence of multiple viruses, including Coxsackie B and Mumps, resulting in a few cases of acute diabetes [47]. It has been previously reported that hyperglycemia acts as an independent risk factor of death in SARS-CoV-infected patients [48]. The coupling of the virus to the ACE2 receptor may result in the impairment of the function of ACE2, and the loss of function of this enzyme is reported to cause DM, as observed in ACE2 KO mice [49]. Moreover, the virus can also use the ACE2 as its receptor to be able to get inside the pancreatic islets for replications, causing damage to the pancreatic islet cells, such as the insulin-producing beta cells. This will subsequently lead to insulin deficiency, a direct cause of acute DM, as noted in SARS-CoV-infected patients [50].

5. Limitations

Our study has several limitations, and thus, our findings should be interpreted with caution. First, a meta-analysis could not be conducted due to the scarcity of relevant data in the included studies. Second, the populations studied were clinically heterogeneous (some studies included adult patients and others included pediatric populations). Third, the differences in the timing of conducting the study, as well as the country in which the study was conducted, could be responsible for the variations in the reported findings due to the variations in the burden of COVID-19 in different regions. Fourth, the majority of included studies were not designed primarily to estimate the prevalence of new-onset T1DM in COVID-19 patients. Fifth, the small sample size of most included studies made it difficult to reach definitive conclusions. Finally, the radiographic findings of such patients are not properly investigated in the available evidence, and the quality of all included studies was low. Therefore, more studies of larger sample sizes are still warranted to reach a definitive conclusion.

6. Conclusions

Based on available evidence, the prevalence of T1DM in patients with COVID-19 ranged from 0.15% to 28.98%. The most common presentation of COVID-19 in patients with T1DM included fever, elevated blood glucose, dry cough, nausea and vomiting, and diabetic ketoacidosis. The outcomes of COVID-19 in terms of length of hospital stay, hospitalization, ICU admission, DKA rate, and severe hypoglycemia were reported variably in the included studies. Due to the heterogeneous study populations and the presence of many limitations, more studies are still warranted to reach a definitive conclusion.

References

[1] World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19. 11 March 2020 [Internet]. WHO Director General's speeches, https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19—11-march-2020; 2020. 4.
[2] World Health Organization. Naming the coronavirus disease (COVID-19) and the virus that causes it [Internet]. World Health Organization; 2020. p. 1. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/naming-the-coronavirus-disease-(covid-2019)-and-the-virus-that-causes-it.
[3] Yang Y, Peng F, Wang R, et al. The deadly coronaviruses: the 2003 SARS pandemic and the 2020 novel coronavirus epidemic in China. J Autoimmun 2020;109:102434.
[4] World Health Organization. Modes of transmission of virus causing COVID-19. 2020. p. 19—21 (March).
[5] Chan JF, Yuan S, Kok KH, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. Lancet (London, England) 2020;395(10223):514—23.
[6] Management CDC. Of patients with confirmed 2019-nCoV | CDC [internet]. Coronavirus disease 2019 (COVID-19). Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html; 2020.
[7] Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet (London, England) 2020;395(10223):497—506.
[8] Pal R, Yadav U, Grover S, Saboo B, Verma A, Bhadada SK. Knowledge, attitudes and practices towards COVID-19 among young adults with Type 1 Diabetes Mellitus amid the nationwide lockdown in India: a cross-sectional survey. Diabetes Res Clin Pract 2020;166:108344.
[9] Ruan S. Likelihood of survival of coronavirus disease 2019. Lancet Infect Dis 2020;20(6):630—1.
[10] DiMeglio LA, Albanese-O'Neill A, Muñoz CE, Maahs DM. COVID-19 and children with diabetes-updates, unknowns, and next steps: first, do No extrapolation. Diabetes Care 2020;43(11):2631—4.
[11] Koliaki C, Tentolouris A, Eleftheriadou I, Melidonis A, Dimitriadis G, Tentolouris N. Clinical management of diabetes mellitus in the era of COVID-19: practical issues, peculiarities and concerns. J Clin Med 2020;9(7).
[12] Verma A, Rajput R, Verma S, Balania VKB, Jangra B. Impact of lockdown in COVID 19 on glycemic control in patients with type 1 Diabetes Mellitus. Diabetes Metab. Syndr. 2020;14(5):1213—6.
[13] d'Annunzio G, Maffeis C, Cherubini V, et al. Caring for children and adolescents with type 1 diabetes mellitus: Italian Society for Pediatric Endocrinology and Diabetology (ISPED) statements during COVID-19 pandemia. Diabetes Res Clin Pract 2020;168:108372.
[14] Rabbone I, Schiaffini R, Cherubini V, Maffeis C, Scaramuzza A. Has COVID-19 delayed the diagnosis and worsened the presentation of type 1 diabetes in children? Diabetes Care 2020;43(11):2870—2.
[15] Singhai K, Swami MK, Nebhinani N, Rastogi A, Jude E. Psychological adaptive difficulties and their management during COVID-19 pandemic in people with diabetes mellitus. Diabetes Metab Syndr: Clin Res Rev 2020;14(6):1603—5.
[16] Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6(7):e1000097.
[17] Health Nlo. National institutes of health quality assessment tool for observational cohort and cross-sectional studies. 2016.
[18] Al Hayek AA, Robert AA, Alotaibi ZK, Al Dawish M. Clinical characteristics of hospitalized and home isolated COVID-19 patients with type 1 diabetes. Diabetes Metab Syndr 2020;14(6):1841—5.
[19] Barron E, Bakhai C, Kar P, et al. Associations of type 1 and type 2 diabetes with COVID-19-related mortality in England: a whole-population study. Lancet Diabetes Endocrinol 2020;8(10):813—22.
[20] Cariou B, Hadjadj S, Wargny M, et al. Phenotypic characteristics and prognosis of inpatients with COVID-19 and diabetes: the CORONADO study. Diabetologia 2020;63(8):1500—15.
[21] Holman N, Knighton P, Kar P, et al. Risk factors for COVID-19-related mortality

in people with type 1 and type 2 diabetes in England: a population-based cohort study. Lancet Diabetes Endocrinol 2020;8(10):823–33.
[22] Li J, Wang X, Chen J, Zuo X, Zhang H, Deng A. COVID-19 infection may cause ketosis and ketoacidosis. Diabetes, Obesity and Metabolism 2020;22(10):1935–41.
[23] Pla B, Arranz A, Knott C, et al. Impact of COVID-19 lockdown on glycemic control in adults with type 1 diabetes mellitus. J Endocr Soc 2020;4(12):bvaa149.
[24] Unsworth R, Wallace S, Oliver NS, et al. New-onset type 1 diabetes in children during COVID-19: multicenter regional findings in the U.K. Diabetes Care 2020;43(11):e170–1.
[25] Ebekozien OA, Noor N, Gallagher MP, Alonso GT. Type 1 diabetes and COVID-19: preliminary findings from a multicenter surveillance study in the U.S. Diabetes Care 2020;43(8):e83–5.
[26] Vamvini M, Lioutas VA, Middelbeek RJW. Characteristics and diabetes control in adults with type 1 diabetes admitted with COVID-19 infection. Diabetes Care 2020;43(10):e120–2.
[27] Yang J-K, Jin J-M, Liu S, et al. New onset COVID-19-related diabetes: an indicator of mortality. medRxiv; 2020.
[28] Atlas G, Rodrigues F, Moshage Y, Welch J, White M, O'Connell MA. Presentation OF paediatric type 1 diabetes IN Melbourne, Australia during the initial stages OF the COVID-19 pandemic. J Paediatr Child Health 2020;56(10):1654–5.
[29] Bhatti R, Omer A, Khattib S, Shiraz S, Matfin G. Clinical characteristics and outcomes in diabetes patients admitted with COVID-19 in Dubai: a cross-sectional single centre study. medRxiv; 2020.
[30] O'Malley G, Ebekozien O, Desimone M, et al. COVID-19 hospitalization in adults with type 1 diabetes: results from the T1D exchange multi-center surveillance study. J Clin Endocrinol Metab 2021;106(2). https://doi.org/10.1210/clinem/dgaa825.
[31] Barron E, Bakhai C, Kar P, et al. Associations of type 1 and type 2 diabetes with COVID-19-related mortality in England: a whole-population study. Lancet Diabetes Endocrinol 2020;8(10):813–22.
[32] Vamvini M, Lioutas VA, Middelbeek RJW. Characteristics and diabetes control in adults with type 1 diabetes admitted with COVID-19 infection. Diabetes Care 2020;43(10):e120–2.
[33] Bhatti R, Omer A, Khattib S, Shiraz S, Matfin G. Clinical characteristics and outcomes in diabetes patients admitted with COVID-19 in Dubai: a cross-sectional single centre study. medRxiv; 2020.
[34] Al Hayek AA, Robert AA, Alotaibi ZK, Al Dawish M. Clinical characteristics of hospitalized and home isolated COVID-19 patients with type 1 diabetes. Diabetes Metab. Syndr. 2020;14(6):1841–5.
[35] Di Dalmazi G, Maltoni G, Bongiorno C, et al. Comparison of the effects of lockdown due to COVID-19 on glucose patterns among children, adolescents, and adults with type 1 diabetes: CGM study. BMJ Open Diabetes Res Care 2020;8(2).
[36] Rabbone I, Schiaffini R, Cherubini V, Maffeis C, Scaramuzza A. Has COVID-19 delayed the diagnosis and worsened the presentation of type 1 diabetes in children? Diabetes Care 2020;43(11):2870–2.
[37] Pla B, Arranz A, Knott C, et al. Impact of COVID-19 lockdown on glycemic control in adults with type 1 diabetes mellitus. J Endocr Soc 2020;4(12):bvaa149.
[38] Yang J-K, Jin J-M, Liu S, et al. New onset COVID-19-related diabetes: an indicator of mortality. medRxiv; 2020.
[39] Unsworth R, Wallace S, Oliver NS, et al. New-onset type 1 diabetes in children during COVID-19: multicenter regional findings in the U.K. Diabetes Care 2020;43(11):e170–1.
[40] Cariou B, Hadjadj S, Wargny M, et al. Phenotypic characteristics and prognosis of inpatients with COVID-19 and diabetes: the CORONADO study. Diabetologia 2020;63(8):1500–15.
[41] Atlas G, Rodrigues F, Moshage Y, Welch J, White M, O'Connell MA. Presentation OF paediatric type 1 diabetes IN melbourne, Australia during the initial stages OF the COVID-19 pandemic. J Paediatr Child Health 2020;56(10):1654–5.
[42] Holman N, Knighton P, Kar P, et al. Risk factors for COVID-19-related mortality in people with type 1 and type 2 diabetes in England: a population-based cohort study. Lancet Diabetes Endocrinol 2020;8(10):823–33.
[43] Ebekozien OA, Noor N, Gallagher MP, Alonso GT. Type 1 diabetes and COVID-19: preliminary findings from a multicenter surveillance study in the U.S. Diabetes Care 2020;43(8):e83–5.
[44] Di Dalmazi G, Maltoni G, Bongiorno C, et al. Comparison of the effects of lockdown due to COVID-19 on glucose patterns among children, adolescents, and adults with type 1 diabetes: CGM study. BMJ Open Diabetes Res Care 2020;8(2).
[45] Kumar A, Arora A, Sharma P, et al. Is diabetes mellitus associated with mortality and severity of COVID-19? A meta-analysis. Diabetes Metab. Syndr. 2020;14(4):535–45.
[46] Rubino F, Amiel SA, Zimmet P, et al. New-onset diabetes in covid-19. N Engl J Med 2020;383(8):789–90.
[47] Jaeckel E, Manns M, Von Herrath M. Viruses and diabetes. Ann N Y Acad Sci 2002;958:7–25.
[48] Yang JK, Feng Y, Yuan MY, et al. Plasma glucose levels and diabetes are independent predictors for mortality and morbidity in patients with SARS. Diabet Med : J Br Diabetic Assoc 2006;23(6):623–8.
[49] Niu MJ, Yang JK, Lin SS, Ji XJ, Guo LM. Loss of angiotensin-converting enzyme 2 leads to impaired glucose homeostasis in mice. Endocrine 2008;34(1–3):56–61.
[50] 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(3):193–9.