January 2022

Interactions Between Diabetes And Covid-19: A Scoping Review

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Abstract

Background: The COVID-19 pandemic that started in March 2020 caused by the SARS-CoV-2

virus introduced an incredible number of unknowns that ongoing research aims to investigate.

One such unknown is the relationship between diabetes and COVID-19. Existing literature has

identified diabetes as a risk factor for poor health outcomes in COVID-19 patients, however,

other information is limited and inconclusive.

Objective: There are two primary goals of this scoping review. First, to consolidate existing

literature about both associations between COVID-19 and diabetes, and the biological

mechanisms of how diabetes and COVID-19 may interact. This includes consolidating

information about diabetes as a risk factor for contracting COVID-19, diabetes as a risk factor

for poor health outcomes in those infected with COVID-19, diabetic management during social

distancing, long-term symptoms in diabetic patients previously infected with COVID-19, and the

potential for new-onset diabetes as a long-term impact of COVID-19 infection. The second goal

of the review is to identify current gaps in knowledge and research.

Methods: Literature was selected from PubMed using specific inclusion and exclusion criteria.

After the selection process, the remaining literature was summarized and information from all of

the literature reviewed was categorized based on the theme.

Results: The initial searches yielded 428 results, and after filtering based on the criteria, there

were 95 results remaining. After reviewing the abstracts for the 95 results, 13 articles were

ultimately selected to be included in the scoping review based on relevancy to diabetes and

COVID-19.

Conclusion: There is insufficient research to draw any definitive conclusions about whether

diabetes is a risk factor for contracting COVID-19. Diabetes is a risk factor for poor health

outcomes including hospitalization and mortality for those infected with COVID-19. Poorer

diabetes management during social distancing may have reduced glycemic control among

diabetic patients. There is a potential risk of developing new-onset Type 1 diabetes after

COVID-19 infection. Existing literature has primarily focused on diabetes as a risk factor for

poor health outcomes in patients with COVID-19 and the biological mechanisms of how diabetes

and SARS-CoV-2 interact. Further research should be conducted to learn more about diabetes as

a risk factor for contracting COVID-19, diabetes self-management during social distancing, and

long-term symptoms of patients with diabetes.

Acknowledgments

I would first like to express my most heartfelt gratitude to my thesis advisor, Dr. Nicola Hawley, for being an incredibly patient and encouraging mentor. Without Dr. Hawley's continual support, this thesis would not have existed, and truly no words will be able to encompass how appreciative I am. I would also like to thank my second reader, Dr. Tracy Rabin, for being so accommodating and stepping in to help complete this thesis. The YSPH faculty offers a unique and genuine warmth that I had never previously experienced before, and I am grateful for the community that they have provided. Finally, I would like to thank friends and family members who have been by my side each step of the way. My grandmother, Dr. Kumudini Joshi, my parents, Arundhati and Vijay Topkar, and my dog, Gypsy, have been my greatest supporters and they are the ones that inspired my interest in public health.

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<u>Introduction</u>

COVID-19 Overview

Since December 2019, the coronavirus disease (COVID-19) caused by SARS-CoV-2 virus has been a global health emergency. COVID-19 is a highly infectious respiratory disease that was first discovered in late 2019 but has produced a multitude of virus variants. The high basic reproductive value (R_0) of 2-4 in addition to asymptomatic transmission has allowed COVID-19 to cause a full global pandemic since March 2020 [4]. There have been over 6 million deaths directly caused by COVID-19 and almost 500 million confirmed cases worldwide as of April 2022 [1]; however these figures, though significant, do not encompass all of the damage that the pandemic has caused. Unreported COVID-19 cases and deaths, deaths attributable to a lack of resources, and long-term COVID-19 symptoms are only a few of the impacts unaccounted for. As further research is conducted about COVID-19, more information is revealed about risk factors, impacts, etc.

The SARS-CoV-2 virus infects the body when the virus spike protein binds to the angiotensin-converting enzyme 2 (ACE2) receptor, which is found in many cells including cells in the nose, mouth, and lungs [31]. COVID-19 is a respiratory disease because the respiratory system serves as an entryway for the virus to infect the rest of the body. ACE2 normally functions to regulate blood pressure by breaking down angiotensin II, which is a hormone that raises blood pressure via vasoconstriction [31]. This review will refer to the disease caused by the SARS-CoV-2 virus including symptoms and long-term impacts as COVID-19, and will refer to the actual virus that mechanistically interacts with cells as SARS-CoV-2.

Diabetes Overview

Diabetes mellitus is a chronic disease that impacts the ability of a body to produce insulin, which in turn impacts blood sugar levels. Insulin is a hormone produced by beta cells in the pancreas that allows glucose from the blood to transport into the cell to be used for energy. In patients with diabetes, insulin production is significantly reduced which means that glucose cannot be used by cells and remains in the bloodstream. Furthermore, having hyperglycemia, or high blood sugar, as a result of reduced insulin for long periods of time can cause a number of comorbidities including heart disease, stroke, and kidney disease [29]. If not treated or regulated, hyperglycemia can cause diabetic ketoacidosis, in which the body starts to break down fat for energy when sufficient insulin is not available to transport glucose into cells [34]. A byproduct of fat is ketones that can build up in the bloodstream and reduce the overall pH of the blood. Diabetic ketoacidosis can be life-threatening [34].

In 2015, 9.4% of the United States population had diabetes, and over one-quarter of them were unaware that they had diabetes [29]. Patients with diabetes often have comorbidities, including hypertension which is treated by ACE inhibitor drugs that prevent angiotensin I from converting to angiotensin II [31]. There are two main forms of diabetes: Type 1 and Type 2. Patients with Type 1 diabetes cannot produce insulin on their own because their immune systems attack their beta cells. These patients are generally diagnosed at a younger age. Patients with Type 2 diabetes have a reduced ability to produce insulin often due to poor nutrition, low activity levels, and age. These patients are generally diagnosed at an older age, and this form of diabetes is the most common with approximately 92% of adults with diabetes having Type 2 diabetes [29]. There are other forms of diabetes such as gestational diabetes, however, this review will focus primarily on Type 1 and Type 2 diabetes.

Viral Infections and Diabetes

There is existing research on how viral infections such as rotavirus, rubella virus, mumps virus, coxsackievirus B, and cytomegalovirus may put people at a higher risk of developing diabetes. Mechanistically, viral infections induce an immune response that results in antigen presentation, which activates the release of inflammatory cytokines. The role of these cytokines is to recruit, stimulate, and proliferate immune cells to combat viral infection [30]. Specifically, the autoreactive effector T-cell in the immune system, in pursuit of fighting the viral infection, can damage or destroy beta cells that produce insulin. This increases the risk of developing diabetes, especially in those who are already predisposed to diabetes. Repeated viral infection further increases this risk [15]. Similarly, increased viral load will yield a greater cytokine response, which may progress into a cytokine storm. A cytokine storm can be life-threatening because the immune system will aggressively attack the body's tissues and organs-even to a fatal point [32]. This kind of immune response is dangerous under any condition, but particularly for patients with diabetes who may sustain too much damage to the pancreas which would further reduce insulin production [32].

Existing Literature

The current literature available can be classified into two main categories:

1. Reported potential associations between diabetes and COVID-19 (ex. "Patients with diabetes are at higher risk of poor health outcomes.")

2. Proposed biological and technical mechanisms of how COVID-19 and diabetes interact (ex. "The SARS-CoV-2 virus binds to the ACE2 receptor.")

Since 2020, research has become progressively more specific as more information about COVID-19 has been discovered. The most recent general scoping review about COVID-19 and diabetes found was in 2020. Other literature has been more specific to certain aspects of COVID-19, which is helpful but not as generalizable. There are minimal recent observational studies or experimental studies since those forms of research require longer periods of time. This scoping review, thus, will fill a missing gap in current knowledge about COVID-19 and diabetes as an overview.

Scoping Review Questions

The primary question guiding this review is:

What literature and knowledge is currently available on the interactions between diabetes and COVID-19, and where are there gaps in the literature?

Secondary questions guiding this review are:

1. How is diabetes a risk factor for contracting COVID-19?

2. How is diabetes a risk factor for poor health outcomes in those infected with COVID-19?

3. How did self-management of diabetes during social distancing change?

4. What are the long-term symptoms in patients with diabetes previously infected with COVID-19?

5. How might COVID-19 infection increase the risk of new-onset diabetes?

Review Objective and Rationale

There are two main objectives for this scoping review.

1. Consolidate existing research about COVID-19 and diabetes into one source.

2. Evaluate potential gaps in research to better recommend future research.

The high rates of both diabetes and COVID-19 present concern for how the two diseases may interact with one another. As a newer area of research, literature about COVID-19 and diabetes is being published at a fast pace to push out as much information as possible. However, there may be certain areas of research that have been prioritized thus far, causing other areas of research to be overlooked. This review aims to summarize the types of literature currently available and potential gaps in knowledge. Furthermore, there is a wide range of information about diabetes and COVID-19 currently available, meaning that it is difficult to understand the topic without significant research. This review can serve as an overview of COVID-19 and diabetes to map key concepts in current literature and be used as a precursor for a systematic review.

Research Design

Rationale for Scoping Review

A scoping review is the most appropriate method to explore existing literature given the minimal information currently available about the topic and the short period of time that information has been available for. Additionally, one of the goals of this review is to consolidate maximal existing knowledge about the interaction between diabetes and COVID-19 in many different contexts, with the understanding that new literature on the topic will continue to be

rapidly released for the foreseeable future. The second goal of this review is to identify gaps in

research overall based on themes identified in the selected literature. Thus, a wider perspective is

necessary. The JBI Manual for Evidence Synthesis was used to justify conducting a scoping

review and as a guide for the format of this review [33]. The Preferred Reporting Items for

Systematic Reviews and Meta-Analyses (PRISMA) 2020 checklist was also used as a guide,

specifically for reporting the results of the review.

Eligibility Criteria:

Inclusion criteria

There were several inclusion criteria: Only literature from January 1st, 2021 onward was

included. This date was arbitrarily chosen, however, meant to signify an appropriate amount of

time since the beginning of the COVID-19 pandemic in March 2020 for recent enough and still

relevant research. All populations, languages, and countries of publication were included due to

limited existing literature. The literature included was from peer-reviewed journals and was

available in full for free. The article type was limited to clinical studies, observational studies,

meta-analyses, and reviews, although existing available literature is primarily reviews. In

accordance with JBI and PRISMA criteria for scoping reviews, these eligibility criteria were

defined a priori. The criteria are also minimally restrictive to allow for greater scope.

Exclusion criteria:

Literature that was published before January 1st, 2021 was excluded. Clinical trials were

excluded from the selection because they are interventional, and the goal of this review is to

understand how COVID-19 and diabetes interact on an observational level rather than

treatments. Literature not readily available in full for free was not included. Furthermore, literature that did not primarily focus on diabetes and COVID-19 was excluded. For example, a study discussing multiple comorbidities including diabetes in the context of COVID-19 was excluded because diabetes during COVID-19 was not the primary subject. This exclusion criterion was enforced during the manual selection process of reviewing abstracts done by the thesis author. This allowed the review to be more specific to the review objectives and removed irrelevant information.

Search Strategy

In accordance with the two main categories of existing literature identified in the review introduction, two separate searches were conducted. The first search started with "COVID-19 AND diabetes mellitus" followed by the keywords found in Table 1 to address the more theoretical associations discussed. The second search started with "SARS-CoV-2 AND hyperglycemia" followed by the keywords found in Table 1 to address the more technical mechanisms discussed.

Table 1 lists the keywords used in the search. However, in filtering the search results, the keywords were also used during the manual abstract review to decide whether the papers retrieved were relevant and specific enough to diabetes and COVID-19 to include. Searches were conducted in PubMed (keywords are provided in Table 1) in April 2022.

Diabetes	COVID-19	Treatment	Outcome
New-Onset Diabetes	Pandemic	Self-Management	Morbidity
Diabetes Mellitus	Viral Infection	Telemedicine	Mortality
Diabetic Ketoacidosis	SARS-CoV-2	Mechanism	Diagnosis
Risk Factor	Post COVID-19 Syndrome		
Type 1/Type 2	Long COVID		
Insulin	COVID-19		
Hyperglycemia			
Comorbidity			

Table 1. Primary keywords of interest in searching for literature and filtering the literature

Search 1:

"COVID-19 AND diabetes mellitus AND (diabetic ketoacidosis OR new-onset diabetes OR type 1 OR type 2 OR insulin OR hyperglycemia OR comorbidity) AND (pandemic OR infection OR SARS-CoV-2 OR post COVID-19 syndrome OR long COVID) AND (self-management OR telemedicine OR mechanism) AND (morbidity OR mortality OR diagnosis)"

Search 2:

"SARS-CoV-2 AND hyperglycemia AND (diabetic ketoacidosis OR new-onset diabetes OR type 1 OR type 2 OR insulin OR diabetes OR comorbidity) AND (pandemic OR viral infection OR COVID-19 OR post COVID-19 syndrome OR long COVID) AND (self-management OR telemedicine OR mechanism) AND (morbidity OR mortality OR diagnosis)"

Selection Process

The selection process for this scoping review included five steps. From the initial search results, the results were filtered based on the date published, article type, free full-text availability, and duplicates from a previous search. The last step of the selection process was reviewing the abstracts of the remaining search results and selecting only the relevant literature that focused primarily on diabetes and COVID-19.

Results

The two searches on PubMed resulted in a collective total of 428 results. After filtering the results by date to exclude literature before January 1st, 2021, there were a total of 261 results. Further filtering of literature not available as a free full text yielded 227 total results, and filtering by article type yielded 107 results. After filtering out duplicates, 95 search results remained. Filtering by article type yielded the greatest exclusion by filtering the results from 227 to 107. This was primarily because a large fraction of the searched literature was reporting case numbers, which was excluded since those reports were time-specific and thus were outdated at the time this review was conducted. A manual filtering process was then used to assess the remaining searches. The abstracts of the 95 results were reviewed by the thesis author and filtered accordingly based on the exclusion criteria quality assessment. The main reason that literature was excluded in this step was because it was too specific or was not in line with the review objectives. Adhering to the review objectives, selection prioritized generalizability to analyze a comprehensive overview on the topic. In total, 13 papers were selected in accordance with the eligibility criteria for this scoping review [Figure 1].

Pubmed Searches

	Search 1	Search 2
Initial Results	361	67
Filtering by Date	220	41
Limit Text Availability	190	37
Limit Article Type	89	18
Remove Duplicates	89	6
Manual Filter (Abstract Review)	11	2

Table 2. The literature selection process yielded 13 total articles in the review.

Analysis

Overall, 13 papers were selected in total for the scoping review. All 13 papers were literature reviews, and all 13 were published within the past 12 months. After summarizing the main points of each paper (Table 4, Table 5), six different themes were identified as commonly discussed in the selected literature. The summaries of the key themes in each paper are provided in Table 3.

Study	Diabetes is a risk factor for contracting COVID-19	Diabetes is a risk factor for poor health outcomes after contracting COVID-19	Diabetes self-management during social distancing	Long-term symptoms patients with diabetes after COVID-19 infection	New-onset diabetes after COVID-19 infection	Biological mechanism linking diabetes and SARS-CoV-2	Total Themes Discussed
Metwally et al.	X	X		X	X		4
Shreshtha et al		X					1
Michalakis K, Ilias I		X			X	X	3
Sabri et al	X	X			X	X	4
Mahrooz et al		X		X	X	X	4
Kazakou et al		X			X		2
Mahmudpour et al		X				X	2
Unnikrishnan et al		X	X	X		X	4
Yonekawa A, Shimono N		X			X	X	3
Roy S, Demmer R		X					1
Srivastava et al		X		X		X	3
Sardu et al.		X	X			X	3
Singh et al		X			X	X	3
Ratio	2/13	13/13	2/13	4/13	7/13	9/13	
Percentage	15.4%	100%	15.4%	30.8%	53.8%	69.2%	

Table 3. Review of which themes were discussed in each of the 13 articles in the review

Table 3 offers insight into areas of study that are currently being prioritized and what research is lacking. All 13 papers discussed diabetes as a risk factor for poor health outcomes after COVID-19 infection and came to similar conclusions. Of the selected literature, 53.8% discussed new-onset diabetes after COVID-19 infection with mixed conclusions, and 69.2% of the selected literature discussed the biological mechanism of interaction between diabetes and COVID-19. Additionally, 30.8% discussed long-term symptoms of COVID-19 among diabetic patients, each of which determined that there is not enough information to draw a conclusion at this point, and 15.4% of the selected literature discussed diabetes as a risk factor for contracting COVID-19.

The studies included in this review reviewed a multitude of article types. Out of the 13 selected articles, 12 included observational studies, 7 included reviews, 6 included meta-analyses, and 2 included experimental studies. In contrast to this review, the articles included literature from 2020 which allowed for a greater range of article type than this scoping review.

Diabetes as a Risk Factor for Contracting COVID-19

Among the papers that discussed this theme, none came to any definitive conclusions. Metwally et al. and Sabri et al. suggest that there is evidence to support that hyperglycemia may increase risk of contracting COVID-19, however, both ultimately conclude that the mechanism of this association is still unclear and further research should be conducted [12, 17.].

Diabetes as a Risk Factor for Poor Health Outcomes after COVID-19 Infection

Every article selected in this review concluded that diabetes is a risk factor for a poor prognosis after COVID-19 infection. These poor health outcomes include hospitalization, long-term symptoms, and mortality [12]. A study in China, also corroborated by a study in England, found that the mortality rate among patients with diabetes who had been infected with COVID-19 was approximately triple that of patients who did not have diabetes [23]. Poor glycemic control was identified as a key risk factor for poor health outcomes after COVID-19 infection in both diabetic and non-diabetic patients [14]. Hyperglycemia severity on the first day a patient is hospitalized for COVID-19 was found to be a strong predictor of prognosis, however, the specific blood glucose levels have not been defined yet [23].

Diabetes Self-Management During Social Distancing

As a result of strict social distancing in response to increased COVID-19 cases, patients with diabetes did not have access to the regular care they previously relied on to manage their diabetes [22]. Poor management of diabetes can increase the risk of COVID-19 poor health outcomes, loss of limbs, and mortality [22]. Telemedicine allowed patients to regularly speak to their providers, but patients could not get their health metrics regularly checked. If further care was needed, it had to be classified as severe enough to warrant a visit to a hospital where resources were extremely limited and the risk of contracting COVID-19 was greater [22].

The pandemic also caused significant changes to lifestyle. Access to adequate nutrition, insulin, and medication was limited because venturing into public spaces increased the risk of COVID-19, especially for patients with diabetes. Overall regular physical activity decreased and stress levels increased, which worsened diabetes management [Unnikrishnan]. The compounded

effect of lifestyle changes and lack of access to care quickly became a significant concern for patients with diabetes.

Long-Term Impact of COVID-19 in Patients with Diabetes

Metwally et al, Mahrooz et al, Unnikrishnan et al, and Srivastava et al. briefly discussed potential long-term symptoms of COVID-19 infection among diabetic patients, but none of them came to a definitive conclusion. Mahrooz et al suggested that diabetes is a risk factor for "long COVID" which includes tiredness, muscle pain, joint pain, and breathlessness. Furthermore, the severity of COVID-19 symptoms may be correlated to risk of new-onset diabetes, and potentially overall immunity [20]. For example, a patient who experienced diabetic ketoacidosis is at higher risk of long-term COVID-19 symptoms and contracting new infections than a patient who experienced mild hyperglycemia [20]. Singh et al. discussed how vaccine immunity may wane quicker in patients with diabetes, which is why vaccinating as many people as possible is so important [19].

New-Onset Diabetes After COVID-19

There has been evidence that new-onset type 1 diabetes is a potential long-term impact of COVID-19 [20]. There is currently insufficient data to draw any conclusions, however, the use of corticosteroids in treating COVID-19, hyperglycemia, and metabolic dysfunction during COVID-19 infection may be associated with new-onset diabetes [17]. Mahrooz et al. and Sabri et al. suggest that while there is evidence to support that COVID-19 infection increases the risk of new-onset diabetes, the mechanisms of this association are still unknown and further research should be conducted [18, 17]. Evidence that viral infections such as rubella may be associated

with new-onset diabetes has been available and accepted for a decade, so there is a biological precedent for new-onset diabetes after COVID-19 infection [12]. It is also plausible that new-onset diabetes is primarily a long-term impact of COVID-19 among people who were already predisposed to a diabetes diagnosis [20]. Yonekawa et al. suggests that COVID-19 may cause glycemic dysregulation even in previously healthy patients, which may result in new-onset diabetes [23] Further research is necessary, however, to make more definitive conclusions.

Diabetes and SARS-CoV-2 Interacting Mechanism

The actual mechanism of why diabetes increases the risk of mortality and other poor health outcomes in patients with COVID-19 is still being studied; however, several potential possibilities have been proposed. In patients with uncontrolled diabetes, hyperglycemia allows an increased rate of SARS-CoV-2 replication. This viral proliferation both increases the severity of COVID-19 and quickens the progression of symptoms [28]. Patients with diabetes who experience hyperglycemia would be administered an increased dose of insulin, which is associated with an increase in cytokines that causes inflammation [28]. This response has the potential to cause a cytokine storm, in which the immune system begins attacking its own tissues, which can be life-threatening.

Another potential outcome of COVID-19 infection is beta cell damage. Appropriate beta-cell function is critical for patients with diabetes because these cells produce insulin. ACE2 receptors where SARS-CoV-2 binds to are expressed in beta cells [14]. Accordingly, SARS-CoV-2 impacts beta-cell function, thus impacting glycemic control [20]. Furthermore, patients with diabetes are often on ACE inhibitor medications to manage co-existing hypertension, however, these medications increase ACE2 expression and thus allow

SARS-CoV-2 greater opportunity to bind, infect, and progress [28]. The reason why diabetic patients infected with COVID-19 are at so much higher risk of poor outcomes is that diabetes worsens COVID-19 and COVID-19 worsens diabetes.

Discussion

Given these thematic breakdowns, it is clear that more research is needed to determine if and how diabetes is a risk factor for contracting COVID-19, how diabetes self-management changed during social distancing, long-term symptoms of COVID-19 among diabetic patients, and new-onset diabetes. Even though 61.5% of the literature discussed new-onset diabetes, the results were inconclusive suggesting that this is an area of research that should be prioritized. By contrast, research about diabetes as a risk factor for poor health outcomes after COVID-19 infection may not need to be prioritized anymore because there is comparatively sufficient and consistent literature that has determined that diabetes is a risk factor.

There are also clear gaps in the types of research being conducted. More recent literature after January 1st, 2021 are primarily reviews. However, based on the articles reviewed in the selected literature, there are very few experimental studies. Furthermore, though 12 of the 13 selected articles included observational studies, these studies were from before 2021. More observational and experimental studies should be conducted moving forward to fill this gap, and provide more recent data.

Conclusion

Limitations

There were several clear limitations to this literature review. First, only reviews were included. This was because most observational studies in the initial search were excluded since they were from 2020. Other more recent observational studies were very specific, which was not in line with the review objective of generalizability. Additionally, observational studies require longer periods of time, meaning that the short timeframe has limited most literature about COVID to reviews.

There is also a limitation on the information consolidated in this review itself due to the timeline of COVID-19. Studies about COVID-19, and furthermore studies about diabetes and COVID-19, are very recent, and more research is needed to draw more definitive conclusions. Especially when evaluating long-term impacts, long periods of time are necessary for follow up. Because of this, minimal clinical data is available, limiting the application of this scoping review. Research is quickly being published, though, and more definitive conclusions can be made once more information is available.

Overall Conclusion and Recommendations

This scoping review has effectively consolidated the existing literature regarding diabetes and COVID-19 and has illuminated where further research is necessary. There is no definitive conclusion if diabetes is a risk factor for contracting COVID-19, how diabetes self-management was impacted during social distancing, long-term symptoms after COVID-19 infection in patients with diabetes, and new-onset diabetes after COVID-19 infection. Accordingly, these are

areas of research that should be prioritized moving forward. Every article selected did conclude that diabetes is a risk factor for poor health outcomes after contracting COVID-19 and there is sufficient evidence to support the proposed biological mechanisms between diabetes and COVID-19. There were no notable discrepancies in conclusions between the selected literature. Although there were varying degrees of confidence in certain conclusions, all authors agreed that at this point no definitive conclusions can be made due to limited information. All of the papers emphasized the importance of further research. Developing novel strains of COVID-19 continue to pose a threat in the pandemic, and research should continue because it is valuable to have the appropriate information in order to develop treatments. As more time passes, greater research will be available about the interaction between COVID-19 and diabetes.

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Appendix

Search 1:

"COVID-19 AND diabetes mellitus AND (diabetic ketoacidosis OR new-onset diabetes OR type 1 OR type 2 OR insulin OR hyperglycemia OR comorbidity) AND (pandemic OR infection OR SARS-CoV-2 OR post COVID-19 syndrome OR long COVID) AND (self-management OR telemedicine OR mechanism) AND (morbidity OR mortality OR diagnosis)"

Study	Date Published	Studies Included	Summary Findings
Metwally et al.	December 2021	Observational, review	- Preexisting diabetes shows higher COVID-19 incidence and outcomes - Higher frequency of diabetes onset and complications after COVID-19 infection - New onset diabetes may be a novel form - New technologies may be used to combat this bidirectional relationship - There is a history of Type 1 diabetes induced by viral infection
Shreshtha et al	September 2021	Observational	- There is a bidirectional relationship between diabetes and COVID-19 - Meta-analysis of observational studies - Increased mortality in hyperglycemic, previously diabetic, and newly diabetic patients compared to those without diabetes - Higher rate of new-onset diabetes and hyperglycemia
Michalakis K, Ilias I	May 2021	Observational, review	- Hyperglycemia can worsen symptoms regardless of diabetes diagnosis - COVID-19 causes inflammation in beta cells, which may increase risk of diabetes
Sabri et al	October 2021	Observational, review, meta-analysis	Lack of beta cells or insulin resistance may be a risk factor for developing COVID-19

			- Diabetic patients often have other comorbidities that put them at higher risk of COVID-19 infection and mortality - Corticosteroid used to treat COVID-19 is associated with new onset diabetes - Insulin resistance may be due to the alternate pathway of SARS-CoV-2 of the RAS
Mahrooz et al	May 2021	Observational, meta-analysis, review	- COVID-19 impacts cellular metabolism, thus decreasing ATP generation - SARS-CoV-2 can cause a cytokine storm - Metabolic dysfunction impacts COVID-19 treatment - Long-term symptoms for diabetic patients recovered from COVID-19 are unknown - COVID-19 may increase risk of new-onset diabetes via metabolic dysfunction
Kazakou et al	February 2022	Observational, experimental, meta-analysis	- Greater risk of poor health outcomes in diabetic patients diagnosed with COVID-19 - COVID-19 may cause metabolic dysregulation and impaired glucose homeostasis - New-onset diabetes after COVID-19 provides evidence of the role of COVID-19 in glucose metabolism
Mahmudpour et al	January 2022	Experimental, observational	- Insulin resistance due to SARS-CoV-2 may cause metabolic deterioration in diabetic patients - There are multiple metabolic pathways that COVID-19 may be disturbing - The diabetes molecular tetrahedron provides a visual representation of the diabetes and COVID-19 relationship, thus yielding more insight into potential therapies
Unnikrishnan R, Misra A	September 2021	Observational, review	- Diabetes is a risk factor for poor health outcomes in COVID-19 patients - Poor glycemic control caused by COVID-19 may be due to pancreatic damage, use of corticosteroids, and cytokine storm

			● Diabetic patients had limited access to care, adequate nutrition, and exercise due to social distancing
Yonekawa A, Shimono N	March 2022	Observational, experimental, meta-analysis, review	● Glycemic state prior to COVID-19 infection may impact risk of new-onset diabetes ● The exact mechanism of why diabetes is a risk factor in COVID-19 patients continues to be investigated ● COVID-19 variants may behave differently in terms of impacting glycemic control
Roy S, Demmer R	March 2022	Observational	● The strength of evidence in COVID-19 and diabetes studies is unknown ● The studies reviewed did not adequately adjust for confounders ● Treating hyperglycemia may not impact COVID-19 outcomes ● Measuring key diabetes biomarkers in non-diabetic patients infected with COVID-19 may be key to treatment
Srivastava et al	March 2022	Observational	● The actual mechanism of why diabetes is a risk factor for COVID-19 patients ● Cytokine storm leads to decreased function of T helper cells ● SARS-CoV-2 binds to ACE-2, which activates the RAS pathway, yielding more inflammation and causing greater insulin resistance ● Inflammatory response could make existing heart conditions worse

Table 4. Summaries of selected literature from search 1.

Search 2:

"SARS-CoV-2 AND hyperglycemia AND (diabetic ketoacidosis OR new-onset diabetes OR type 1 OR type 2 OR insulin OR diabetes OR comorbidity) AND (pandemic OR viral infection OR COVID-19 OR post COVID-19 syndrome OR long COVID) AND (self-management OR telemedicine OR mechanism) AND (morbidity OR mortality OR diagnosis)"

|	Date Published	Studies Included	Summary Findings
Sardu et al.	March 2022	Experimental, meta-analyses, review	• Hyperglycemia is a risk factor for poor health outcomes in COVID-19 patients regardless of diabetes diagnosis • Managing hyperglycemia critical for improving clinical outcomes
Singh et al	March 2022	Meta-analysis, observational	• Diabetes is a risk factor for poor outcomes in COVID-19 patients • Focusing on anti-inflammatory treatment for COVID-19 may reduce poor health outcomes due to diabetes and reduce the potential for new-onset diabetes

Table 5. Summaries of selected literature from search 2.
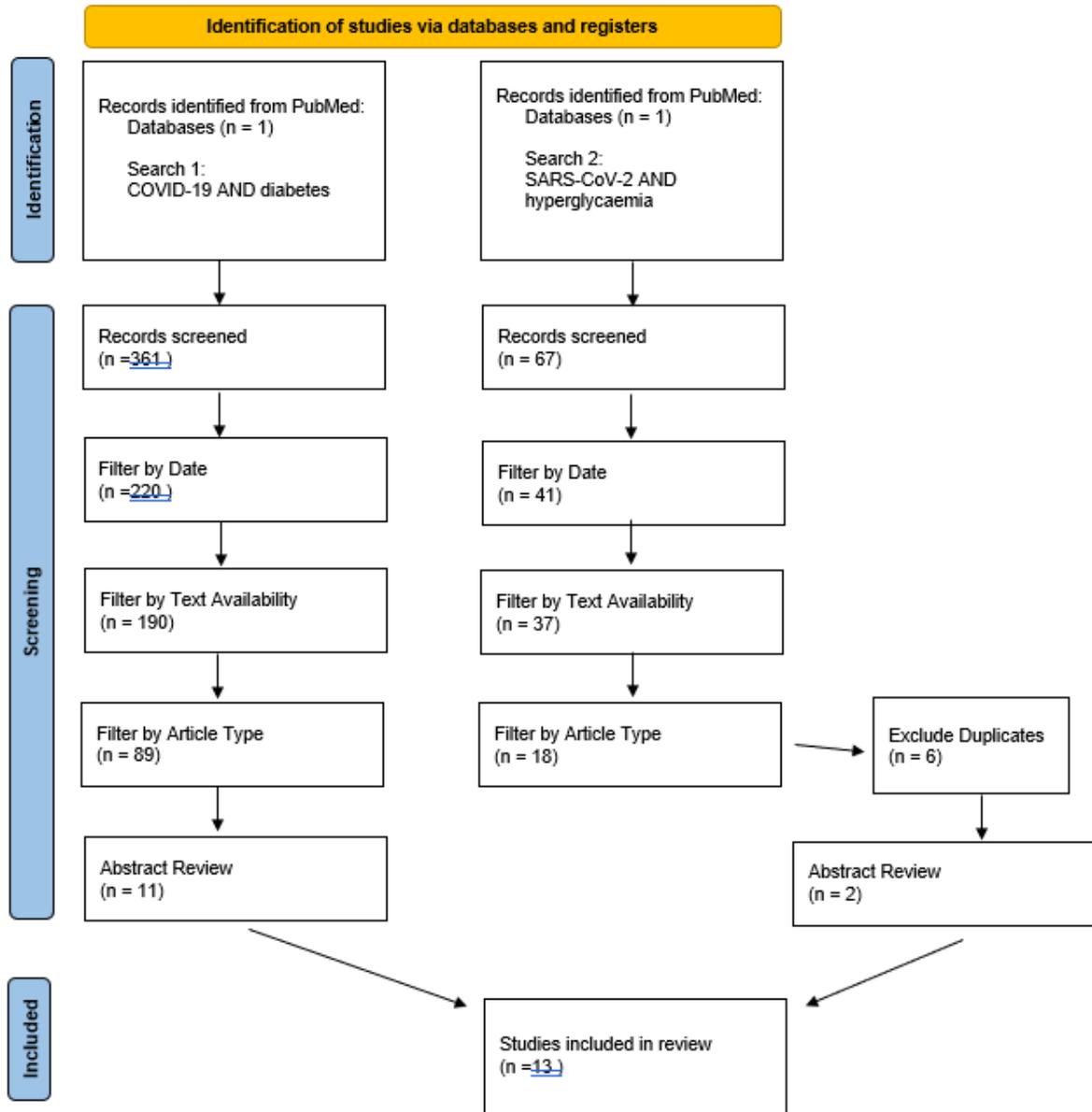
Figure 1. Study selection flow chart [PRISMA]