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.

REVIEW ARTICLE

Impaired glucose regulation, SARS-CoV-2 infections and adverse COVID-19 outcomes

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Impaired glucose regulation (IGR) is common world-wide, and is correlated with Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) the virus that causes Coronavirus disease 2019 (COVID-19). However, no systematic reviews are available on the topic, and little is known about the strength of the evidence underlying published associations. The current systematic review identified consistent, reproducible associations but several limitations were observed including: (1) a consistent lack of robust confounder adjustment for risk factors collected prior to infection; (2) lack of data on insulin resistance or glycemia measures (Hemoglobin A1c (HbA1c) or glucose); (3) few studies considering insulin resistance, glucose or HbA1c values in the clinically normal range as a predictor of SARS-CoV-2 risk; (4) few studies assessed the role of IGR as a risk factor for infection among initially uninfected samples; (5) a paucity of population-based data considering SARS-CoV-2 as a risk factor for the onset of IGR. While diabetes status is a clear predictor of poor prognosis following a SARS-CoV-2 infection, causal conclusions are limited. It is uncertain whether interventions targeting dysglycemia to improve SARS-CoV-2 outcomes have potential to be effective, or if risk assessment should include biomarkers of diabetes risk (ie, insulin and glucose or HbA1c) among diabetes-free individuals. Future studies with robust risk factor data collection, among population-based samples with pre-pandemic assessments will be important to inform these questions. (Translational Research 2022; 241:52–69)

Abbreviations: IGR = Impaired glucose regulation; SARS-CoV-2 = Severe acute respiratory syndrome coronavirus 2; COVID-19 = Coronavirus disease 2019; T2DM = Type 2 Diabetes Mellitus; HbA1c = Hemoglobin A1c; ACE-2 = Angiotensin Converting Enzyme-2; TMPRSS2 = Transmembrane serine protease 2; T1DM = Type 1 Diabetes Mellitus

INTRODUCTION

Diabetes Mellitus is believed to be an important risk factor predisposing to Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes Coronavirus disease 2019 (COVID-19) infection as well as severity of infection and risk for hospitalization and mortality. Interestingly, less is known about the relationships between non-diabetic impaired glucose regulation (for the purposes of this review, prediabetes, and insulin resistance) as a potential risk factor for SARS-CoV-2 infection. For example, Rosenthal et al reported that 29.9% of inpatients with a diagnosis of COVID-19 had no co-morbidities using the

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Charlson-Deyo comorbidity index suggesting the importance of phenotypic characteristics other than comorbidity burden.[1]

One of the key factors in deciphering the above conundrum is to view Type 2 Diabetes Mellitus (T2DM) as a continuum of glucose dysregulation and not merely dichotomously by hyperglycemia exceeding thresholds (largely identified vis-à-vis their prediction of microvascular outcomes).[2] Tabak et al observed a modest linear increase in fasting and post prandial glucose, followed by a sharp rise in the aforementioned levels and a steeper decrease in HOMA insulin sensitivity in the 5 years prior to diagnosis of T2DM, suggesting that individuals with prediabetes are already in the accelerated phase, trending towards overt diabetes.[3] The relative risk of cardiovascular events was 1.33 (95% CI:1.06-1.67) for impaired fasting glucose and 1.58 (95% CI: 1.19-2.10) for impaired glucose tolerance.[4] The current guidelines in the screening, diagnosis, and management of cardiometabolic disease have shifted towards prioritizing risk factors of preclinical entities such as insulin resistance and prediabetes. For instance, the United States Preventive Services Task Force updated their recommendations in 2015 to include screening for diabetes among those ages 40-70 years who are overweight or obese which was previously limited to asymptomatic individuals with hypertension.[5] Similarly, the American Association of Clinical Endocrinologists introduced the dysglycemia based chronic disease model (DBCD) to include stage I of insulin resistance, stage II of biochemical risk or prediabetes, stage III of T2DM, and stage IV vascular complications, to encourage aggressive cardiovascular management as early as stage I.[6] Although uncommon, the microvascular complications of T2DM, specifically retinopathy has been reported in the impaired glucose regulation phase, before diabetes is diagnosed.[7] Therefore, considering impaired glucose regulation as a continuum in relation to SARS-CoV-2 outcomes could add great value to risk prediction as SARS-CoV-2 infection will likely become endemic.[8]

Beyond the role of IGR as a predictor of SARS-CoV-2 infection and poor outcomes post-infection, there is preliminary evidence that SARS-CoV-2 infection itself might be a risk factor for impaired glucose regulation and subsequent diabetes development among diabetes-free individuals. There is a strong rationale to believe this is possible based on the broader literature linking infections to adverse metabolic outcomes including insulin resistance,[9-11] glucose intolerance[12] and diabetes development.[2,13-16]

In this review, we systematically search the literature for published data on the interplay between impaired glucose regulation, diabetes mellitus and SARS-CoV-2. We summarize key findings and discuss a variety of methodological issues and their implications for understanding whether metabolic parameters predict risk of SARS-CoV-2 infection and poor COVID-19 outcomes, as well as the evidence that SARS-CoV-2 induces metabolic abnormalities increasing diabetes risk. We additionally summarize emerging concepts related to the biological plausibility of the relationships.

Table I. PUBMED search equation

1. severe acute respiratory syndrome coronavirus 2
"sars cov 2"(MeSH Terms) OR "sars cov 2"(All Fields) OR "severe acute respiratory syndrome coronavirus 2"(All Fields)
2. SARS COV 2
"sars cov 2"(MeSH Terms) OR "sars cov 2"(All Fields) OR "sars cov 2"(All Fields)
3. COVID 19
"covid 19"(MeSH Terms)
4. Equation: 1 OR 2 OR 3
5. Prediabetes
"prediabetic state"(MeSH Terms) OR ("prediabetic"(All Fields) AND "state"(All Fields)) OR "prediabetic state"(All Fields) OR "prediabetes"(All Fields) OR "prediabetic"(All Fields) OR "prediabetics"(All Fields)
6. Insulin resistance
"insulin resistance"(MeSH Terms) OR ("insulin"(All Fields) AND "resistance"(All Fields)) OR "insulin resistance"(All Fields)
7. Glucose
"glucose"(MeSH Terms) OR "glucose"(All Fields) OR "glucoses"(All Fields) OR "glucose s"(All Fields)
8.Hemoglobin A1C
"glycated hemoglobin a"(MeSH Terms) OR "glycated hemoglobin a"(All Fields) OR ("hemoglobin"(All Fields) AND "a1c"(All Fields)) OR "hemoglobin a1c"(All Fields)
9. Diabetes Mellitus
"diabetes mellitus"(MeSH Terms) OR ("diabetes"(All Fields) AND "mellitus"(All Fields)) OR "diabetes mellitus"(All Fields)
10. Equation 5 OR 6 OR 7 OR 8 OR 9
11. Equation: 4 AND 10

LITERATURE SEARCH STRATEGY

To assess the evidence from population-based and clinically-based human studies, we searched PubMed for literature published on impaired glucose regulation, diabetes, SARS-CoV-2, and COVID-19 between December 2019 and June 2021. The search strategy is summarized in Table I. Initially 3,008 publications were identified. A primary reviewer SR removed duplicate publications and reviewed titles for inclusion. Ambiguous inclusion decisions were discussed by both authors (SR and RTD) to determine inclusion and/or exclusion. Review articles (systematic reviews, meta-analysis), case reports, studies that were done

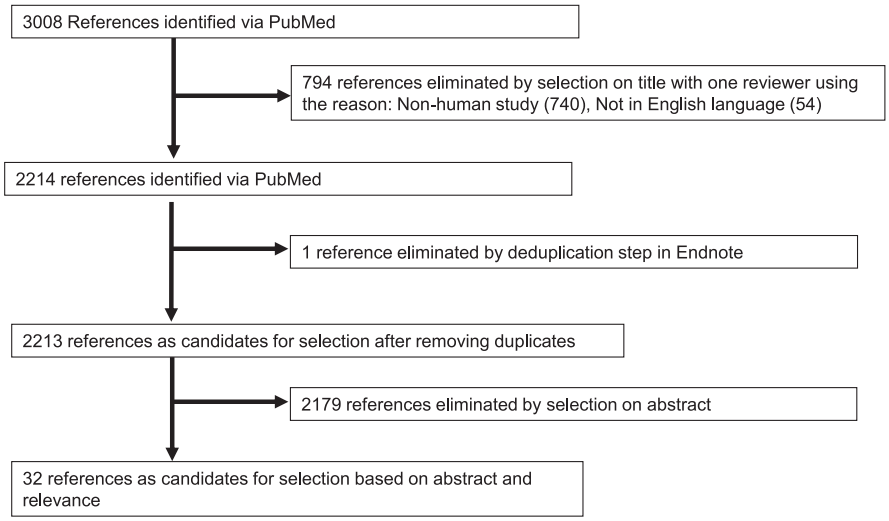

Fig 1. Study selection flow diagram.

exclusively in children and adolescence or in pregnancy and studies that did not report a measure of association pertinent to the specific search criteria were excluded. The final selection flow is summarized in Fig 1 and 32 articles assessing metabolic parameters and SARS-CoV-2 infection were included.

METABOLIC PARAMETERS, INFECTION RISK AND SEVERITY

Diabetes Mellitus and Risk of Infection. Nearly all studies identified included only study samples with SARS-CoV-2 infected patients, while only five studies considered samples with and without SARS-CoV-2 infected individuals. Therefore, limited data exist considering the contribution of diabetes status to the risk of becoming SARS-CoV-2 infected. Among studies that do include samples with and without infection, most report on poor SARS-CoV-2 related outcomes rather than the cumulative incidence of infection. Nevertheless, while sparse, the limited data are informative. McGurnaghan *et al*[17] provide total population level data among 5,463,300 Scotland residents (5.8% with diabetes) and assessed whether diabetes status was associated with critical care unit-treated COVID-19 or mortality. The age and sex adjusted odds ratios for poor COVID outcomes was 2.40[1.82-3.16] among people with T1DM (Type 1 Diabetes Mellitus) and 1.37[1.28-1.47] for people with T2DM (vs diabetes-free individuals). While this study cannot fully address the risk of infection associated with diabetes, it informs the risk for severe infection including mortality among an initially infection-free cohort. In another study among nearly the total population of England, a third of all in-hospital deaths with COVID-19 between March 1 and May 11, 2020, occurred among people with diabetes. Mortality rates were higher among those with diabetes vs those without; T1DM again demonstrated stronger mortality risk than T2DM.[18] Similarly, studies from Mexico,[19] and Italy[20] also reported higher risk of SARS-CoV-2 outcomes (including hospitalization and mortality) among those with vs. without diabetes (Table II).

Diabetes Status and Risk of Poor Outcomes or Mortality. Most published studies to date, included only hospitalized patients with confirmed SARS-CoV-2 infection. Table II provides a summary of all studies and their key design features and findings. In total 26 inpatient studies were identified among which 20 reported mortality outcomes while the remaining 6 reported adverse outcomes such as ICU admission and/or length of stay, need for mechanical ventilation, and/or COVID-19 severity. Reports arose from 11 countries across diverse populations and included 28,311 patients. Reported mortality rates varied greatly but among eight such studies with a samples size of at least 1000, six studies reported mortality rates >20%. Among 13 studies that reported a summary measure of association for mortality, 9 observed a statistically significantly increased risk for death among those with vs. without diabetes. Limited reporting for T1 vs. T2 diabetes was available, although at least one large study with >6000 patients[21] reported empirically higher risk for hospitalization among patients with T1DM (but seemingly equal risk for mortality between T1DM and T2DM). In contrast, a separate study with only 238 patients reported lower mortality risk among T1DM although there was only 1 death in the T1DM group and the findings for both T1DM and T2DM were not statistically significant.

Table II. Summary of studies assessing the association between diabetes mellitus and SARS-CoV-2 infection and/or COVID-19 outcomes

Study	Country	N	Mean Age±SD (range)	Male (%)	Study Design	Diabetes Assessment	Outcome	SARS-CoV-2 Assessment	Study population	Adjustments	Measure of Association (95% Confidence Interval)
Population based studies											
Woolcott *et al.* 2021	Mexico	757,210	44 (33−56)	52%	Cohort study	Self-reported	COVID-19 mortality within 28 days of evaluation	Positive RT-PCR	≥20 years, viral respiratory disease symptoms, screened for SARS-CoV-2 via the System of Epidemiological Surveillance of Viral Respiratory Disease from Jan-Nov, 2020	1,2,5,6a,6c,6d, 6e,6h,19	HR 1.49 (1.47−1.52)-Overall HR 1.66 (1.58−1.74) Outpatients HR 1.14 (1.12−1.16) Hospitalized
Barron *et al.* 2020	UK	61,414,470	41±23	50%	Cohort study	EHR	COVID-related in-hospital mortality	Positive antigen test or if negative, COVID-19 reported as cause of death	All individuals registered with a general practice in England, alive on Feb 16, 2020	1,2,4,7-9	OR 2·86 (2·58-3·18)-T1DM OR 1·80 (1·75-1·86)-T2DM
Dennis *et al.* 2021	UK	19,256	67	60%	Cohort study	England Surveillance System (CHESS)	In-hospital mortality	Positive RT-PCR of nasopharyngeal and/or oropharyngeal swabs	Hospitalization due to COVID-19 requiring admission to a high dependency unit (HDU) or intensive care unit (ICU) from March- July 2020, excluding pregnancy	1-5,6(a-h)	HR 1.23, (1.14, 1.32)
McGurnaghan *et al.*2021	UK	5,463,300	NR	NR	Cohort study	National Diabetes Register	Fatal or critical care unit-treated COVID-19	Positive RT-PCR test, a hospital discharge code for COVID-19, or COVID-19 code on death certificate	Total Scottish population at the start of the pandemic on Mar 1, 2020	1,2	OR 1·39 (1·30−1·49)-Overall OR 2·39 (1·81−3·16)-T1DM OR 1·36 (1·27−1·46)-T2DM
Silverii *et al.*2021	Italy	4,969,000	NR	NR	Cohort study	Italian SARS-CoV-2+ Surveillance System	COVID-19 prevalence by diabetes status	testing method not specified	Total population of Sicily	1,2	RR 0.92 (0.79-1.09)
		159	73±13				COVID-19 mortality		All SARS-CoV-2 positive cases	1,2	RR 4.5 (3.55-5.71)-DM

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Table II. (*Continued*)

Study	Country	N	Mean Age±SD (range)	Male (%)	Study Design	Diabetes Assessment	Outcome	SARS-CoV-2 Assessment	Study population	Adjustments	Measure of Association (95% Confidence Interval)
CDC COVID-19 Response Team	USA	7,162	NR	NR	MMWR Report	Documented in case report form	COVID-19	Laboratory confirmed COVID-19	Data of COVID-19 cases reported to CDC from 50 states, four U.S. territories and affiliated islands, the District of Columbia, and New York City from Feb−Mar,2020	1[†]	Prevalence n(%) 784, (10.9)
Hospital based studies											
Collard *et al.* 2021	Netherlands	1604	66±15	61%	Cohort study	EHR/ antidiabetic medication	Mortality during first 21 days following admission	Positive COVID-19 PCR or high suspicion based on CT-imaging of the thorax.	Multi-center, Dutch CovidPredict cohort	1,2,5,6d,19	HR 1.93 (1.43-2.62)- ≥2 antidiabetic HR 1.25(0.9-1.74)-1 antidiabetic. (Ref-No Diabetes)
Altunok *et al.* 2021	Turkey	722	57±15	51%	Cohort study	NR	Mortality	Positive nasopharyngeal RT-PCR with chest CT findings compatible with COVID-19 pneumonia	Single center, patients with laboratory and chest CT confirmed COVID-19 pneumonia b/w Mar-May, 2020	None	OR-1.97 (0.71-5.41)
Klonoff *et al.* 2021	USA	1544	64±16	54%	Cohort study	Severe hyperglycemia: BG>13.88 mmol/L	Mortality	COVID-19−positive laboratory test	Multi-center, patients with COVID-19 from Glytec national database from 91 hospitals in 12 states.	1,2,10,13,15	Severe hyperglycemia Non-ICU: HR 7.17 (2.62−19.62)- day 2-3 glucose HR 1.46 (0.68-3.14)- glucose on admission ICU: HR 1.40 (0.53−3.69)- day 2-3 glucose HR 3.14 (1.44-6.88)- glucose on admission Ref: BG <7.77 mmol/L (140 mg/dL)
Liu *et al.* 2021	China	77	64±4	62%	Cohort study	HbA1c ≥6.5%	Mortality	Positive RT−PCR	Hospitalized patients with confirmed COVID−19-identified as severe cases or critically ill cases at admission.	1,14,18,20,24	HR 1.57 (1.15−2.15)

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Table II. (*Continued*)

Study	Country	N	Mean Age±SD (range)	Male (%)	Study Design	Diabetes Assessment	Outcome	SARS-CoV-2 Assessment	Study population	Adjustments	Measure of Association (95% Confidence Interval)
Liu, Ye *et al.* 2021	China	233	64	49%	Cohort study	Self-reported/ HbA1c on admission ≥ 48 mmol/ mol	Mortality	Two clinical manifestations of COVID-19 and positive RT-PCR nasopharyngeal samples	Single center study, patients admitted from Jan-Apr, 2020	None	Diabetes: HR 2.64 (1.14-6.11) Hba1c ≥ 6.5% HR 5.80 (1.32, 25.53) Ref: Hba1c 5.7-6.4% FPG ≥ 7.0 HR 12.64 (2.93, 54.48) 5.6-6.9 HR 3.49 (0.73, 16.82) Ref: ≤ 5.5
Li *et al.* 2020	China	453	61 (49-68) *	57%-known DM 61%-newly diagnosed	Cohort study	H/O Diabetes, fasting glucose ≥7mmol/L and/or HbA1c ≥6.5% on admission	Mortality	Exposure to confirmed SARS-CoV-2 infection or to Wuhan Huanan seafood market	Patients admitted with laboratory−confirmed SARS−Cov−2 infection from Jan-Mar, 2020.	1,2,19,47-53	Newly diagnosed diabetes HR 5.63 (1.22-26) Known diabetes HR 8.76 (1.78-43.2)
Sourij *et al.* 2021	Austria	238	71±13	64%	Cohort study	Diabetes diagnosed according to the Austrian Diabetes Association guidelines.	Mortality	Positive throat swab for SARS−CoV−2	Patients with diabetes hospitalized with COVID-19.	None	OR 1.85 (0.66−5.16) -T2DM OR 0.46 (0.44−4.90) -T1DM
Mamtani *et al.* 2021	USA	403	55	68%	Cohort study	Hyperglycemia: (one blood glucose value ≥7.78 mmol/L during hospitalization. Diabetes: HbA1c ≥6.5%	Mortality	Positive PCR for the RdRp and N genes	Single center, COVID-19 patients hospitalized from March-May 2020	1,27-32	Diabetes/no-hyperglycemia OR 5.97 (0.32−111.8) Diabetes/hyperglycemia OR 17.06 (3.46−84.1). (Ref: No Diabetes/No hyperglycemia)
Nafakhi *et al.* 2020	Iraq	192	60±10	43%	Cohort study	HbA1c >6.5%, h/o diabetes, on antidiabetic medication	COVID-19 pneumonia related length of ICU stay, hospital stay, lung injury, in-hospital death	Positive RT-PCR -nasopharyngeal swab and clinical symptoms of COVID-19 along with CT scan to assess pneumonia severity	Single center, patients diagnosed with COVID-19 pneumonia at the outpatient clinic or admitted from Aug-Oct 2020	1,20,27,41[%]	Insulin use OR 0.4 (0.3-5)-lung injury Metformin use OR 0.1(0.1−0.6)-in hospital death OR -0.3(0.2−4)- length of ICU stay OR -0.4 (0.2−3)-Length of hospital stay DDP-4 OR -0.3(0.2-3)-length of ICU stay

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Table II. (*Continued*)

Study	Country	N	Mean Age±SD (range)	Male (%)	Study Design	Diabetes Assessment	Outcome	SARS-CoV-2 Assessment	Study population	Adjustments	Measure of Association (95% Confidence Interval)
Al-Salameh *et al.* 2021	France	433	72±14-DM 71± 16-non-DM	55%	Cohort study	EHR, HbA1c ≥48 mmol/mol on admission	Primary endpoint: admission to ICU and/or death.	Positive RT-PCR-nasopharyngeal swab	Single center, patients hospitalized with COVID-19	1,2,5,6a,6,c, 6d,6e,6i, 11,12,13, 15,16,17,21,22	OR 1.12 (0.66-1.90)-Primary endpoint OR: 2.06 (1.09-3.92)-ICU admission HR 0.73 (0.40-1.34)- Mortality
Fox *et al.* 2021	USA	355	66 ± 14	51%	Cohort study	Patients on antidiabetic medication prior to admission	Composite outcome of inpatient mortality, need for renal replacement therapy/hemodialysis, intubation, and vasopressors	Positive RT-PCR-nasopharyngeal swab	Single-center, COVID-19 positive patients, admitted from Mar-Apr 2020	1,2,3,15,6b-e,6i-k	OR 1.4 (0.84 to 2.31)
Kim *et al.* 2021	USA	2,491	62 (50-75) *	53%	Cohort study	EHR	a) In-hospital mortality b) ICU admission	Resided in a predefined surveillance catchment area; positive SARS-CoV-2 test within 14 days prior to/during hospitalization	Coronavirus Disease 2019-Associated Hospitalization Surveillance Network	a)1,2,3,4,5,6c-h,19,22. b) 1,2,3,4,5,6c-h 6l-m,19	a) Risk ratio 1.19 (1.01−1.40) in-hospital mortality b) Risk ratio: 1.13 (1.03−1.24)-ICU admission
Orioli *et al.* 2020	Belgium	345	69 ± 14	48%	Cohort study	Known or newly diagnosed diabetes (HbA1c ≥ 6.5% on admission)	Mortality	Positive RT-PCR and/or SARS-CoV-2 pneumonia on admission (infiltrates on either chest x-ray or chest-CT)	Single center study, patients with known or newly diagnosed diabetes and confirmed COVID-19 from Mar-May,2020	6d,54,55	HR 0.43 (CI 0.16−1.17)
Tchang *et al.* 2021	USA	3,533	65(53−77) *	59%	Cohort study	EHR/ HbA1c ≥ 6.5%.	Composite outcome: ICU admission, invasive mechanical ventilation, or in−hospital mortality	Positive RT-PCR	Patients admitted to New York Presbyterian hospital network, between Mar-May 2020	1,2,3,6a,6c,6d,6e,19	HR 1.15 (1.01−1.30)
Wang *et al.* 2021	China	2433	60(50−68) *	50%	Cohort study	EHR	Disease progression and mortality	Positive RT-PCR or serum IgM-IgG antibody detection	Single center study of all COVID-19 positive between Feb-Apr, 2020	1,17,18,20,27, 30,32,34,36,37[@]. 1,32,34a,38[@@]	Blood glucose (Ref: 3.9−6.1 mmol/L) Outcome of Disease progression[@] > 6.1 mmol/L HR 1.58 (1.25-1.98) < 3.9 mmol/L HR 1.65 (0.97-2.81) Outcome of mortality [@@] > 6.1 mmol/L HR

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Table II. (*Continued*)

Study	Country	N	Mean Age±SD (range)	Male (%)	Study Design	Diabetes Assessment	Outcome	SARS-CoV-2 Assessment	Study population	Adjustments	Measure of Association (95% Confidence Interval)
											3.22 (1.54-6.73) < 3.9 mmol/L HR 7.31 (0.00, inf)
Wang *et al.* 2020	China	605	59(47-68) *	53%	Cohort study	EHR/FBG≥7.0 mmol/L	28-day mortality and in hospital complications	Positive RT-PCR	Multicenter study, Patients hospitalized with COVID-19 from Jan-Feb 2020	1,2,40[$]	28-day mortality[$] HR 2.30 (1.49-3.55) 28-day in hospital complications OR 3.99 (2.71, 5.88) (Ref:FBG <6.1 mmol/l)
Petrilli *et al.* 2020	USA	2741	63(51-74)*	61%	Cohort study	EHR	critical illness, defined as a composite of care in the ICU, use of mechanical ventilation, discharge to hospice, or death	Positive RT-PCR	Patients tested for SARS-Cov-2 between Mar-Apr 2020	1,2,3,4,14, 15,17,19,20, 24,34b,38,44	OR 1.38 (1.17 to 1.62) (Unadjusted) OR 1.23(0.99-1.5) (Adjusted)
Cheng *et al.* 2021	China	407	48	48%	Cohort study	Fasting glucose ≥ 7.0 mmol/L; 2 hr PP/random glucose ≥ 11.1 mmol/L	ICU admission, Invasive ventilation	Positive RT-PCR in suspected cases with H/O contact with the Wuhan area or with confirmed cases in the last 14 days)/ fever and/or respiratory tract symptoms /radiological features of pneumonia	Multicenter study, patients admitted from Jan-April 2020	1 and 23**	ICU admission OR 0.04 (0.00- 0.99)-Preadmission metformin use ** OR 1.02 (0.98−1.05)-Preadmission insulin OR 0.53 (0.18−1.61)-In-hospital metformin OR 1.02 (0.98−1.05)-In-hospital insulin Invasive ventilation Pre-admission metformin-0.09 (0.00−1.80) Pre-admission insulin-1.03 (1.00−1.07) In-hospital metformin-0.34 (0.07−1.62) In-hospital insulin 1.04 (0.99−1.09) **
Gregory *et al.* 2021	USA	6,451	T1DM 37(21−51) *T2DM 58 (49−97) *	T1DM-42% T2DM-56%	Cohort study	T1DM-H/O autoantibodies or required multiple daily injections. T2DM-on antidiabetic medications	Hospitalization and illness severity	Positive RT-PCR	Epic Clarity data warehouse (houses entire EHR at VUMC, a network of 137 primary care, urgent care, and hospital facilities b/w Mar-Aug 2020.	1,2,3,6c,15,19	Hospitalization OR 3.90 (1.75−8.69) -T1DM OR 3.36 (2.49−4.55) -T2DM (Ref- No Diabetes) Illness severity OR 3.35 (1.53−7.33)-T1DM OR 3.42 (2.55−4.58)- T2D (Ref- No Diabetes)

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Table II. (*Continued*)

Study	Country	N	Mean Age±SD (range)	Male (%)	Study Design	Diabetes Assessment	Outcome	SARS-CoV-2 Assessment	Study population	Adjustments	Measure of Association (95% Confidence Interval)
Vargas-Vázquez *et al.* 2020	Mexico	317	57(47–64) *	NR	Cohort study	DM: previous diagnosis and/or treatment with glucose-lowering agents. Undiagnosed: if HbA1c ≥6.5% De novo/ intrahospital hyperglycemia if FPG ≥140 mg/dL without diabetes and normal HbA1c	Severe COVID-19: composite of death/ICU admission/mechanical ventilation	Positive RT-PCR	Hospitalized patients from a Mexico City reference center	1,2,15,26	Undlagnosed T2DM OR: 7.91 (2.59-28.07) Previously diagnosed T2DM OR:3.14 (1.12 10.31) De novo-OR 4.36 (1.53 to 13.67) but not associated with mortality after covariate adjustment
Koh *et al.* 2021	Singapore	1,042	39±11	95%	Cohort study	EHR, HbA1c ≥6.5%	4 outcomes: a) Severe COVID−19 (SpO2 ≤93% on room air, respiratory rate ≥30 24 or need for ICU care) b) Dyspnea c) ICU admission. d) length of stay	Positive RT−PCR throat/nasopharyngeal swab	Single center study with patients admitted from Feb-May 2020	1,2,15,17,42	a) HR: 2.71 (1.34−5.47) b) HR 2.34 (1.13−4.88) c) 6.15 (1.99−19.05) d)1.70 (0.51−2.88)
Mithal *et al.* 2021	India	401	54(19−92) *	69%	Cross-sectional study	H/O diabetes or HbA1c ≥ 6.5%.	a) ICU admission b) mortality c) COVID-19 disease severity score (using WHO ordinal scale for clinical improvement)	Positive RT-PCR-nasopharyngeal swab	Single center, patients hospitalized with COVID-19	None	DM versus no DM a) 24.3 vs 12.3%, p-0.002 b)6.3 vs 1.4%, p-0.015 c) 20.1 vs 9%, p-0.002. Baseline Hba1c (n = 331) with severity scores (r = 0.136, p = 0.013).
Tang *et al.* 2021	China	197	66(7−76) *	61%	Cohort study	Not reported	Disease aggravation	Positive RT-PCR/ serum IgM-IgG antibody	Single center, patients hospitalized with COVID-19 from Jan-Mar 2020.	1,2,6c,11,14, 17,18,20,24, 27, 33-39	27/88 (30.7%) with disease aggravation were diabetic OR 8.31 (2.92−23.6)

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Table II. (*Continued*)

Study	Country	N	Mean Age±SD (range)	Male (%)	Study Design	Diabetes Assessment	Outcome	SARS-CoV-2 Assessment	Study population	Adjustments	Measure of Association (95% Confidence Interval)
Zhang *et al.* 2020	China	312	57 (38-66) *	45%	Cohort study	FPG ≥7.0 mmol/L/self-reported physician-diagnosed diabetes/anti-diabetic medication use. Newly diagnosed diabetes: Patients with no H/O diabetes with FPG ≥7.0 mmol/L at hospital admission	a) composite endpoint events (including mechanical ventilation, admission to intensive care unit, or death) b) mortality c) mechanical ventilation	Positive RT-PCR/serum IgM-IgG antibody	Multicenter study, Patients hospitalized with COVID-19 from Jan-Mar 2020	1,2,12,43-46	a) HR 2.18 (0.89−5.31) b) HR 6.87 (1.92−24.58) c)2.31 (0.76−7.03)
Zheng *et al.* 2021	China	71	63±10-DM 54±14-no DM	64%-DM 38%-no DM	Cohort study	EHR	a) CD4+ T cell% b) CD8+ T cell %. c)IL-6, IL-2, IL-10, and INF-γ d) average hospitalization days	Positive RT-PCR -throat swab/CT findings of COVID-19/SARS-CoV-2 IgM/IgG antibody	Single center study, with COVID positive inpatients from Feb-Mar 2020	15	a)51.75 ± 4.45‡,§ b) 20.95 ± 7.61‡ c) upregulation† d)13 (9, 17.50) ‡,§

ARDS, Acute respiratory distress syndrome;
Adjustments: 1=Age; 2=Sex; 3=Race; 4=Ethnicity; 5=Obesity; 6=Comorbidities; 6a=chronic respiratory disease 6b=Asthma; 6c=HT; 6d=chronic heart disease/cardiovascular disease/CAD; 6e=chronic renal disease;
6f=chronic liver disease; 6g=chronic neurological disease; 6h=Immunosuppression; 6i=COPD; 6j=heart failure; 6k=Atrial fibrillation; 6l=hematological disorders; 6m=rheumatologic/autoimmune disorder;
7=deprivation; 8=geographical region; 9=previous hospital admissions with coronary heart disease, cerebrovascular disease, or heart failure; 10=History of diabetes; 11=LFT; 12=eGFR; 13=glucose on admission;
14=NT−proBNP (per 100 pg/mL); 15=BMI; 16=History of cancer;17=CRP; 18=LDH (per 100 U/L); 19=smoking; 20=Lymphocyte count (per 1 × 109/L); 21=WBC count; 22=Treatment with ACE/ARB's; 23=blood glucose;
24=Serum ferritin (per 100 μg/L); 25=HbA1c; 26=Number of comorbidities; 27=Differential neutrophil count; 28=Hematuria; 29=Initial serum globulin (g/L); 30=Fever with chills; 31=Marijuana use;
32=Platelet count (x109 cells/L); 33=CD3, CD4, CD8; 34=Coagulation function (34a, Fbg; 34b, D dimer); 35=IL-6; 36=Chest distress/dyspnea/chest tightness; 37=BUN; 38=Creatinine kinase; 39=CTnI;
40=CRB-65 measures the severity of pneumonia on a 0 to 4 scale; 41=QTc prolongation; 42=≥2 comorbidities; 43=Prothrombin time; 44=Procalcitonin; 45=aspartate aminotransferase (AST);
46=hospital; 47=systolic blood pressure; 48=total cholesterol; 49=antihypertensive drugs, lipid-lowering agents; 50=admission to ICU; 51=invasive mechanical ventilation;
52=glucose-lowering medication before and during hospital admission; 53=corticosteroid use; 54=cognitive impairment;55=Area of lung injury>50%
*Median (IQR);
†composite of risk factors including diabetes was the exposure; % adjustment with each outcome based on $P < 0.05$
‡versus no DM $P < 0.05$
§versus IFG $P < 0.05$;

Two studies with sample sizes sufficient for subgroup analyses observed that the mortality risk among people with vs. without diabetes, decreased as age increased. Woolcott et al[19] reported adjusted hazard ratios for death to 3.12 (2.86-3.40) for patients 20-39 years of age compared to 1.11 (95% CI 1.06-1.16) for patients 80 years of age or older (*P*-value for interaction<0.05). Similarly, Dennis et al[22] observed adjusted hazard ratios for mortality among patients with vs. without diabetes to be 1.50(1.05-2.15), 1.29 (1.10-1.51), and 1.18(1.09-1.29) among patients aged 18-49, 50-64, and 65+ respectively (*P*-value for interaction<0.05). These interactions could be biologically driven although the underlying mechanisms are unclear. Alternatively, these findings are quite possibly a consequence of scaling as the measures of association were relative risk measures and not absolute risk differences. Regardless, despite attenuated relative risk in the oldest age groups, risk remained elevated among patients with vs. without diabetes and absolute risk for poor outcomes in older, SARS-CoV-2 infected patients with diabetes is quite high.

Impaired glucose regulation and SARS-CoV-2. There were nine studies identified that assessed impaired glucose regulation and SARS-CoV-2 infection (Table III). The criteria used to define impaired glucose regulation varied considerably making between study comparisons challenging. Some studies used objective laboratory parameters while others relied on self-report physician diagnosis. Even among studies relying on laboratory measures, there was variation in the analyses (eg, fasting blood glucose, HbA1c, and triglyceride and glucose index) and thresholds defining IGR. Most studies reported outcomes to be worse among patients with non-diabetic IGR vs metabolically normal patients. However, study samples were small with seven of nine studies enrolling fewer than 500 patients and statistical significance was lacking in several reports.

METHODOLOGICAL LIMITATIONS OF EXISTING STUDIES

Selection Bias. Many of the studies in this review included only hospitalized patients. Such studies are potentially susceptible to differential selection bias according to diabetes status. In some settings, it is possible that – all else equal – patients with diabetes are potentially more likely to be tested for SARS-CoV-2 and/or admitted as the result of perceived higher risk. This could result in a bias such that the risk profile of admitted DM patients was more favorable compared to non-DM patients who perhaps required more severe infection for admission. Such bias could attenuate study findings. While selection bias is a separate issue from confounding, it is possible to mitigate these biases analytically through statistical adjustment if sufficient data collection is available[23] particularly on factors related to prognosis. Given the limited adjustment in most studies, selection bias is a concern that remains to be addressed in future studies.

Information Bias Vis-à-vis SARS-CoV-2 Case Definitions. The assessment method for SARS-CoV-2 infection varied across studies. Most studies defined infection as physician diagnosed with a positive nasopharyngeal and/or oropharyngeal swab RT-PCR confirmed infection. However, several studies (particularly those from early in the pandemic when testing capacity was limited) often relied on physician diagnosis based on symptomology and radiological findings suggestive of SARS-CoV-2 infection. Information bias of this nature is likely to bias study findings towards the null as the SARS-CoV-2 positivity rates during most of the pandemic has been <50% and frequently <5% among symptomatic individuals.[24]

No studies were identified that considered asymptomatic SARS-CoV-2 infection. The lack of population-based research that systematically monitors for any infection (asymptomatic or otherwise) is a major limitation in the literature to date. In the context of risk factor studies, such as those considering metabolic parameters as a risk factor for SARS-CoV-2 infection, mildly symptomatic and asymptomatic infections can bias study results by misclassifying participants as uninfected when in fact they were truly infected but not diagnosed. This form of classical information bias in epidemiological studies will generally bias towards the null if it occurs equally among those with vs. without the risk factor of interest (eg, diabetes).

It remains poorly understood whether asymptomatic cases are more or less likely to occur among individuals with IGR. This is in part due to the need for costly serial testing to enhance the likelihood of detecting asymptomatic and/or mildly symptomatic cases, since gold-standard PCR testing can only detect active viral infection. To address this issue, an alternative to frequent (∼weekly) PCR testing, is less frequent antibody (∼bi-monthly) testing to assess recent history of infection. While promising, important limitations to this approach also remain. For example, the lack of definitive knowledge about the duration of antibody responses coupled with the large number of assays available with substantial performance variability is an important current limitation.[25] Additionally, lack of data related to antibody response and duration that might be differential by IGR status is another important concern. Ironically, while antibody studies might be

Table III. Summary of studies assessing the association between non-diabetic impaired glucose regulation and SARS-CoV-2 infection and/or COVID-19 outcomes

Study	Country	N	Mean Age±SD (range)	Male (%)	Study design	Prediabetes/IFG assessment	Outcome	SARS-CoV-2 Assessment	Study population	Adjustments	Measure of Association (95% Confidence Interval)
Mamtani *et al.* 2021	USA	403	55	68%	Cohort study	Hyperglycemia (atleast one blood glucose ≥7.78 mmol/L during hospitalization with no history of diabetes	Mortality	Positive PCR for the RdRp and N genes.	Single center study, COVID-19 patients hospitalized from March-May 2020	1,27-32	OR 21.94 (4.04−119.0)
Wang*et al.* 2020	China	605	59 (47-68)*	53%	Cohort study	EHR/FBG 6.1-6.9 mmol/l	28-day mortality and in hospital complications	Laboratory-confirmed in accordance with the interim guidance formulated by the WHO	Multicenter study, Patients hospitalized with COVID-19 from Jan-Feb 2020	1,2,40[$]	28-day in hospital complications OR: 2.61 (1.64, 4.41) 28-day mortality[$] HR 1.71 (0.99, 2.94) Ref:FBG <6.1 mmol/l
Zhang *et al.* 2020	China	312	57 (38-66)*	45%	Cohort study	IFG - glucose b/w 5.6 -6.9 mmol/L.	a) composite endpoint events (including mechanical ventilation, admission to ICU/death) b) mortality c) mechanical ventilation	Positive RT-PCR of nasopharyngeal swab or positive serum specific IgM and IgG antibody	Multicenter study, Patients hospitalized with COVID-19 from Jan-Mar 2020	1,2,11,12, 43-46	a) 1.21 (0.43−3.39) b) HR 4.06 (1.00−16.42) c) 0.95 (0.25−3.66)
Sourij *et al.* 2021	Austria	238	71±13	64%	Cohort study	HbA1c 39-46 mmol/mol	Mortality	Positive throat swab for SARS−CoV−2	Hospitalized, with COVID-19, and either diabetes/prediabetes	None	Prediabetes: 14.9% versus Diabetes:26.7% (p=0.128)
Li *et al.* 2020	China	453	61 (49-68)*	53%	Cohort study	Hyperglycemia (fasting glucose 5.6-6.9 mmol/L and/or HbA1c 5.7-6.4%)	Mortality	Exposure to confirmed SARS-CoV-2 infection or to the Wuhan Huanan seafood market.	Patients admitted with lab−confirmed SARS−Cov−2 infection from Jan-Mar 2020.	1,2,19,47-53	HR: 2.64 (0.50-14)
Ren *et al.* 2020	China	151	59±16	52%	Cohort study	EHR-Triglyceride and glucose index (TyG)-marker for insulin resistance	Severe covid 19 infection and mortality	Severe: 1. respiratory rate > 30/min, 2. oxygen saturation ≤ 93%, 3. PaO2/FiO2, 4. Patients developed either with shock, or respiratory failure requiring mechanical ventilation, or combined with the other organ failure admission to ICU	Hospitalized with COVID-19, from Jan-Feb,2020	1,2,17,26, 31	OR 2.9 (1.2-6.3)- severity OR 2.9 (1.2-6.7)-for mortality

(*continued on next page*)

Table III. (*Continued*)

Study	Country	N	Mean Age±SD (range)	Male (%)	Study design	Prediabetes/IFG assessment	Outcome	SARS-CoV-2 Assessment	Study population	Adjustments	Measure of Association (95% Confidence Interval)
Vargas-Vázquez *et al.* 2020	Mexico	317	57 (47−64)*	NR	Cohort study	using HbA1c ADA criteria	Severe COVID-19: composite of death, ICU admission or mechanical ventilation	Positive RT-PCR	Hospitalized patients from a Mexico City reference center	1,2,15,26	OR 3.25 (1.20-10.46)
Koh *et al.* 2021	Singapore	1,042	39±11	95%	Cohort study	EHR, HbA1c 5.7−6.4%	Severe COVID-19	Positive RT−PCR throat/nasopharyngeal swab	Single center study with patients admitted from Feb-May,2020	1,2,15,17, 42	HR: 0.49 (0.11−2.24)
Zheng *et al.* 2021	China	71	61±14(IFG) 54± 14(no DM)	44% (IFG) 38% (no DM)	Cohort study	EHR	Hospitalization days, mortality	Positive RT-PCR -throat swab or typical CT findings of COVID-19 or SARS-CoV-2 IgM/ IgG antibody	Single center study, with COVID positive inpatients from Feb-Mar 2020	15	IFG no different than normal for hospitalization days, or mortality.

Adjustments: 1=Age; 2=Sex; 3=Race; 4=Ethnicity; 5=Obesity; 6=Comorbidities; 6a=chronic respiratory disease 6b=Asthma; 6c=HT; 6d=chronic heart disease/cardiovascular disease/CAD; 6e=chronic renal disease;
6f=chronic liver disease; 6g=chronic neurological disease; 6h=Immunosuppression; 6i=COPD; 6j=heart failure; 6k=Atrial fibrillation; 6l=hematological disorders; 6m=rheumatologic/autoimmune disorder;
7=deprivation; 8=geographical region; 9=previous hospital admissions with coronary heart disease, cerebrovascular disease, or heart failure; 10=History of diabetes; 11=LFT; 12=eGFR; 13=glucose on admission;
14=NT−proBNP (per 100 pg/mL); 15=BMI; 16=History of cancer;17=CRP; 18=LDH (per 100 U/L); 19=smoking; 20=Lymphocyte count (per 1 × 109/L); 21=WBC count; 22=Treatment with ACE/ARB's; 23=blood glucose;
24=Serum ferritin (per 100 μg/L); 25=Hba1c; 26=Number of comorbidities; 27=Differential neutrophil count; 28=Hematuria; 29=Initial serum globulin (g/L); 30=Fever with chills; 31=Marijuana use;
32=Platelet count (x109 cells/L); 33=CD3, CD4, CD8; 34=Coagulation function (34a,Fbg; 34b,D dimer); 35=IL-6; 36=Chest distress/dyspnea/chest tightness; 37=BUN; 38=Creatinine kinase; 39=CTnI;
40=CRB-65 measures the severity of pneumonia on a 0 to 4 scale; 41=QTc prolongation; 42=≥2 comorbidities; 43=Prothrombin time; 44=Procalcitonin; 45=aspartate aminotransferase (AST);
46=hospital; 47=systolic blood pressure; 48=total cholesterol; 49=antihypertensive drugs, lipid-lowering agents; 50=admission to ICU; 51=invasive mechanical ventilation;
52=glucose-lowering medication before and during hospital admission ; 53=corticosteroid use; 54=cognitive impairment;55=Area of lung injury>50%
[a]Median (IQR).

conceptually helpful for identifying prior asymptomatic infections, if their performance is dependent on IGR status, their use would simply lead to another form of differential misclassification bias. Published data on this topic are conflicting with at least one study suggesting antibody response to be similar[26] among those with vs. without diabetes while another study reported impaired seroconversion[27] in diabetes (which would lead to SARS-CoV-2 under-estimation in diabetes). Finally, in the age of vaccination, assays that can reliably distinguish natural infection from vaccination based on serology, will be necessary.[28] Ultimately, while reliance on antibody assays alone could be problematic, their use in combination with other assessment methods could enhance sensitivity of infection identification methods.

CONFOUNDING

All studies included in this review were observational study designs which are susceptible to confounding, in which associations between IGR status and either SARS-CoV-2 infection, or poor COVID-19 outcomes, might be spurious and due to differential distributions of causal risk factors for outcomes among those with vs. without IGR. The epidemiological study design that is least susceptible to confounding is a randomized controlled trial. However, for hypotheses of IGR status as a risk factor for infection and infection severity, RCTs are not possible as the IGR status in humans cannot be randomized. Therefore, well conducted observational studies will be necessary to inform causality. Of central importance to addressing this limitation is the robust data collection of including important potential confounders. The relevant data collection likely extends beyond standard data available in medical records and includes information on lifestyle. As importantly, many of these factors should be assessed prior to infection (and prior to pandemic times) to ensure that baseline risk is rigorously characterized (Fig 2.).

Overall, the level of confounder adjustment observed in most reported studies (Tables II and III) was quite limited. For example, only one-third of studies adjusted for either adiposity or smoking and fewer adjusted for both. Lack of adiposity adjustments is particularly concerning given the early data that adiposity is likely a strong risk factor for diabetes, as well as for hospitalization and death [29] among patients diagnosed with COVID-19. (Fig 2) Similarly, rigorous adjustment for medication use was also limited. Xian *et al* demonstrated in mouse models, the anti-inflammatory role of metformin via inhibition of the NLRP3 inflammasome and interlekin-1β induced acute respiratory distress syndrome in SARS-CoV-2 infection.[30] Similarly statins such as simvastatin and lovastatin were found to be most effective in severe SARS-CoV-2 infection exerting its influence via cytotoxic T lymphocytes and regulatory T cell induction.[31] As the literature assessing the effect of medications targeting dysglycemia,

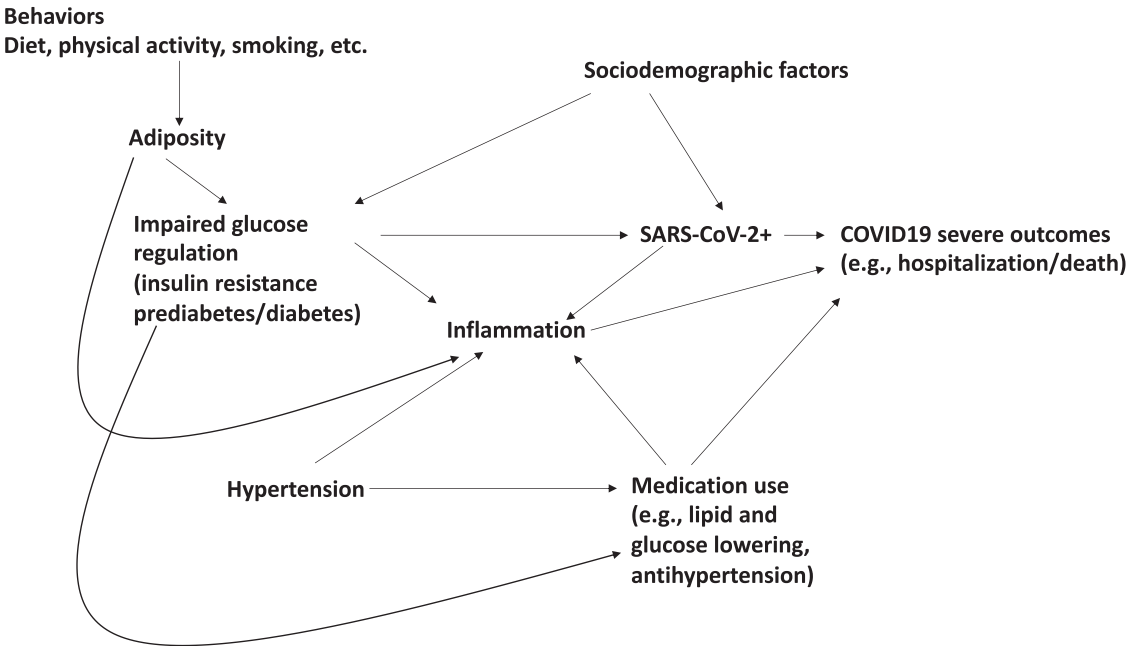

Fig 2. Directed Acyclic Graph summarizing possible causal pathways linking behaviors, biomarkers, IGR, comorbidities to SARS-CoV-2 infection and severity.

hypertension, thrombosis,[32] and hypercholesterolemia on SARS-CoV-2 infection and severity tends to suggest modest protection against infection and mortality, future studies will be enhanced by accounting for medications to avoid negative confounding towards the null (eg, weaker associations due to the protective effect of medications being more common among patients with vs. without diabetes). The need for more robust consideration of several additional important factors including socio-demographic (access to care, income, education, isolation), behavioral (diet, activity), (Fig 2) and biological (d-dimer, blood pressure, renal function) was also largely lacking in published studies limiting interpretation and conclusions.

OVERVIEW OF BIOLOGICAL PLAUSIBILITY LINKING SARS-COV-2 AND METABOLIC ABNORMALITIES

Impaired glucose regulation contributing to SARS-CoV-2 infection. The systematic review discussed above supports the preliminary mechanistic evidence linking IGR to risk for infection as briefly discussed below.

First, SARS-CoV-2 is postulated to bind to ACE-2 (Angiotensin Converting Enzyme-2) receptor which is found on human lung epithelium, vascular endothelium, intestinal lining, pancreatic beta cells etc.[12] ACE-2 works in conjunction with the cell surface protein, Transmembrane serine protease 2 (TMPRSS2), facilitating cellular entry of SARS-CoV-2,[33] resulting in an increased viral load in patients with impaired glucose regulation. Once the virus enters, the S protein activates Desintegrin and metalloproteinase domain 17 (ADAM 17) which has been postulated to increase insulin resistance[34] as well as downregulate surface ACE-2 receptor expression. The current literature on receptor expression on the pancreatic cells is still under speculation. For instance, Lau *et al* demonstrated via RT-PCR and western blot in mouse pancreatic cells, the distribution of ACE, angiotensin 1 (AT-1) and angiotensin 2 (AT-2). The authors concluded that ACE, AT-1, AT-2, and angiotensinogen were expressed in endogenous islets while AT-1 was localized to pancreatic beta cells.[35] On the other hand, Liu *et al*, illustrated that ACE-2 was expressed both in exocrine gland and islet cells. In support of these findings, pancreatic injury in the form of elevated amylase and lipase levels, along with radiological evidence of localized enlargement of the pancreas as well as pancreatic duct dilatation was observed in patients infected with SARS-CoV-2.[36] Another study looked at ACE-2 and TMPRSS2 expression in the islets of Langerhans which was observed via fluorescence stain of five histologically healthy human pancreas. The expression of ACE-2 varied among different cells of the pancreas. For example, TMPRSS2 was detected mainly in endocrine cells, to a lesser extent in the ductal cells and uncommon in the acinar cells. Overall, this study demonstrated insulin secretory granules in beta cells were impaired in those infected with SARS-CoV-2 along with impaired glucose mediated insulin secretion. They were able to demonstrate that the infected islet cells stained positive for endocrine markers (PDX1, NKX6.1) but were negative for insulin indicative of susceptibility of the islet's cells to SARS-CoV-2 infection.[37] However, conflicting evidence exists with one study observing that ACE-2 is mainly expressed on exocrine cells and islets of the pancreas while TMPRSS2 is expressed on ductal cells, diminishing the earlier hypothesis of co-expression of both receptors on islet cells.[38] Taneera *et al* demonstrated that although pancreatic islets expressed ACE-2 and TMPRSS2 irrespective of diabetes status, ACE-2 expression was increased in diabetes, while upregulation of TMPRSS2 was only observed in obese individuals and those with elevated Hba1c levels alone.[39] Future studies are needed to fully understand the synergistic role of these receptors resulting in disruption of glucose homeostasis for identifying risk factors as well as effective management of SARS-CoV-2 infection.

Secondly, diabetes has shown to significantly alter cell-mediated immunity[40,41] lowering the chemotactic and phagocytic function leading to a diminished response to infection. For example, impaired interferon production (IFN-alpha and IFN-gamma) was observed in non-obese diabetic and prediabetic mouse models.[42] Another hypothesized mechanism is that elevated glucose levels increase adherence of microorganisms to cellular receptors,[43] thereby increasing the prevalence of infections in patients with diabetes. Increased SARS-CoV-2 viral replication and cytokine expression were also observed in monocytes of diabetic and/or obese patients in an environment of elevated glucose levels.[44] Codo *et al* observed that the hypoxia-inducible factor 1 alpha(HIF1A) was overexpressed in the monocytes of SARS-CoV-2 infection in greater intensity that that of RSV or influenza-infected monocytes.[44] This might explain the severity of COVID-19 infection and poorer outcomes commonly reported in patients with diabetes.[45] The concurrent responses resemble that of the severe and prolonged infective period observed in MERS-CoV infected mice models with diabetes.[46]

Despite, a reasonable biological premise for IGR to increase risk for poor outcomes among SARS-CoV-2 infected individuals, future studies are necessary to: (1) confirm biological mechanisms in animal models and extend findings to humans; (2) identify biomarker phenotypes that identify elevated risk; and (3) translate

these findings to interventional approaches that reduce infection risk and improve outcomes post-infection.

SARS-CoV-2 infection as a contributor to impaired glucose regulation. There are also several biologically plausible mechanisms through which SARS-CoV-2 might predispose to the development of impaired glucose regulation (as opposed to the reverse). Key mechanisms discussed to date are outlined below.

Chronic inflammation is a plausible biological mechanism linking infections and insulin resistance. Animal models have shown that inflammatory cytokines such as TNF-α can induce a state of insulin resistance,[47] possibly as a consequence of TNF-α's ability to interrupt serine phosphorylation of IRS-1,[48] and data in humans have repeatedly shown inflammation to be an independent risk factor for both insulin resistance[49] and T2DM.[50-52] If a chronic inflammatory phenotype emerges in some COVID-19 patients, it is plausible that insulin resistance may follow along with increased risk for incident prediabetes of diabetes. Notably, in studies that lack pre-infection phenotyping, it is not possible rule out reverse causality (i.e., SARS-CoV-2 induced IGR rather than IGR increase risk for infection and poor outcomes).

SARS-CoV-2 induction of endothelial dysfunction is another potential mechanism underlying poor metabolic outcomes among individuals with symptomatic COVID-19. Evidence is accumulating suggesting that SARS-CoV-2 causes endothelial dysfunction.[53] Importantly, endothelial dysfunction is believed to directly contribute to insulin resistance, possibly by impairing transcapillary passage of insulin to target tissues.[54] This primarily occurs through viral infection induced activation of the integrated stress response pathway (ISR). Phosphorylation of the IRS1 receptor by IRS regulator, PKR kinases, can attenuate insulin action, leading to insulin resistance.[55]

Tropisms for beta-cells is another mechanism linking infection to metabolic abnormalities.[37,56,57] Very recent evidence suggests that SARS-Cov-2 can infect human beta-cells leading to morphological, transcriptional, and functional changes such as reduced insulin-secretory granules and reduced glucose stimulated insulin secretion.[37,56] Accordingly, numerous prior studies have hypothesized a variety of viral infections in the etiology of T1DM due to beta-cell infection and impairment.[58] In support of this notion, impaired glucose metabolism and acute-onset diabetes have been reported to be higher among those with SARS coronavirus 1 pneumonia as compared to individuals with non-SARS pneumonia.[59]

Most of the aforementioned suggested mechanisms linking infection to incident IGR are based on conceptual models, animal models or are extrapolated from other infection models. Although much of the data available stems from animal models, there is insufficient evidence demonstrating SARS-CoV-2 infection causes abnormal glucose levels and findings to date are limited to involvement of the respiratory system and transient systemic inflammation.[60] Moreover, limited human data are available explicitly testing whether SARS-CoV-2 infection increases risk for incident IGR in the short or long-term. As research on Post-Acute Sequelae of SARS-CoV-2 infection (PASC) emerges, studies informing metabolic outcomes will be important for identifying at risk populations requiring careful monitoring and screening.

CONCLUSION

The current literature suggests that a bidirectional relationship between impaired glucose regulation and SARS-CoV-2 infection might exist.

A total of 32 human studies were identified on the topic of IGR as predictor of infection or poor outcomes among infected patients. The majority of studies identified, support the hypothesis that IGR increases risk for poor outcomes among patients with COVID-19. However, few studies addressed risk for infection and even fewer human studies considered SARS-CoV-2 infection as a risk factor for the development of new onset IGR. Additionally, only a limited number of studies considered prediabetes and insulin resistance as possible risk factors for infection. This is an important area of research as SARS-CoV-2 becomes endemic in much of the world for the foreseeable future. In the U.S. context, nearly one in three US adults have prediabetes[61] but limited guidance on infection control measures are available to individuals with prediabetes. As factors such as prediabetes and insulin resistance are modifiable, they are potential targets for reducing the burden of SARS-CoV-2 and setting vaccination policy vis-à-vis patient priority. Additionally, future studies need to account for the use of medications commonly used among patients with prediabetes or diabetes to obtain clear estimates of risk.

Although most research to date supports bidirectional relationships between impaired glucose regulation and SARS-CoV-2 infection and outcomes, several of the aforementioned limitations preclude strong conclusions and future studies are necessary to more rigorously form causal conclusions and prevention-oriented policy. Doing so will not only benefit the clinical management of patients with SARS-CoV-2 but also the broader public health effort to reduce the burden of infection on population health.

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