ISSN 1948-9358 (online)

World Journal of *Diabetes*

World J Diabetes 2023 June 15; 14(6): 632-938

Published by Baishideng Publishing Group Inc

World Journal of Diabetes

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ABOUT COVER

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AIMS AND SCOPE

The primary aim of *World Journal of Diabetes* (*WJD*, *World J Diabetes*) is to provide scholars and readers from various fields of diabetes with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJD mainly publishes articles reporting research results and findings obtained in the field of diabetes and covering a wide range of topics including risk factors for diabetes, diabetes complications, experimental diabetes mellitus, type 1 diabetes mellitus, type 2 diabetes mellitus, gestational diabetes, diabetic angiopathies, diabetic cardiomyopathies, diabetic coma, diabetic ketoacidosis, diabetic nephropathies, diabetic neuropathies, Donohue syndrome, fetal macrosomia, and prediabetic state.

INDEXING/ABSTRACTING

The *WJD* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports/Science Edition, PubMed, PubMed Central, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database. The 2022 Edition of Journal Citation Reports® cites the 2021 impact factor (IF) for *WJD* as 4.560; IF without journal self cites: 4.450; 5-year IF: 5.370; Journal Citation Indicator: 0.62; Ranking: 62 among 146 journals in endocrinology and metabolism; and Quartile category: Q2.

RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Diabetes

ISSN
ISSN 1948-9358 (online)

LAUNCH DATE
June 15, 2010

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Lu Cai, Md. Shahidul Islam, Michael Horowitz

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/1948-9358/editorialboard.htm

PUBLICATION DATE
June 15, 2023

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

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https://www.wjgnet.com/bpg/gerinfo/242

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https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
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World Journal of Diabetes

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World J Diabetes 2023 June 15; 14(6): 892-918

DOI: 10.4239/wjd.v14.i6.892

ISSN 1948-9358 (online)

SYSTEMATIC REVIEWS

Correlation between COVID-19 vaccination and diabetes mellitus: A systematic review

Yan-Fei He, Jing Ouyang, Xiao-Dong Hu, Ni Wu, Zhi-Gang Jiang, Ning Bian, Jie Wang

Specialty type: Endocrinology and metabolism

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Arumugam VA, India; Nooripour R, Iran

Received: December 23, 2022
Peer-review started: December 23, 2022
First decision: March 28, 2023
Revised: April 5, 2023
Accepted: April 24, 2023
Article in press: April 24, 2023
Published online: June 15, 2023

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Abstract

BACKGROUND

Coronavirus disease 2019 (COVID-19) is one of the current global public health threats and vaccination is the most effective tool to reduce the spread and decrease the severity of COVID-19. Diabetes is one of the important chronic diseases threatening human health and is a common comorbidity of COVID-19. What is the impact of diabetes on the immunization effect of COVID-19 vaccination? Conversely, does vaccination against COVID-19 exacerbate the severity of pre-existing diseases in patients with diabetes? There are limited and conflicting data on the interrelationship between diabetes and COVID-19 vaccination.

AIM

To explore the clinical factors and possible mechanisms underlying the interaction between COVID-19 vaccination and diabetes.

METHODS

We conducted a comprehensive search of PubMed, MEDLINE, EMBASE, and *Reference Citation Analysis* (https://www.referencecitationanalysis.com) online datab-ases, and medRxiv and bioRxiv gray literature using the keywords "SARS-CoV-2", "COVID-19", "vaccine", "vaccination", "antibody", and "diabetes" individually or in combination, with a cut-off date of December 2, 2022. We followed inclusion and exclusion criteria and after excluding duplicate public-

ations, studies with quantifiable evidence were included in the full-text review, plus three manually searched publications, resulting in 54 studies being included in this review.

RESULTS

A total of 54 studies were included, from 17 countries. There were no randomized controlled studies. The largest sample size was 350963. The youngest of the included samples was 5 years old and the oldest was 98 years old. The included population included the general population and also some special populations with pediatric diabetes, hemodialysis, solid organ transplantation, and autoimmune diseases. The earliest study began in November 2020. Thirty studies discussed the effect of diabetes on vaccination, with the majority indicating that diabetes reduces the response to COVID-19 vaccination. The other 24 studies were on the effect of vaccination on diabetes, which included 18 case reports/series. Most of the studies concluded that COVID-19 vaccination had a risk of causing elevated blood glucose. A total of 12 of the 54 included studies indicated a "no effect" relationship between diabetes and vaccination.

CONCLUSION

There is a complex relationship between vaccination and diabetes with a bidirectional effect. Vaccination may contribute to the risk of worsening blood glucose in diabetic patients and diabetic patients may have a lower antibody response after vaccination than the general population.

Key Words: COVID-19; Vaccination; Diabetes mellitus; Antibody; Blood glucose; Immune response

Core Tip: Coronavirus disease 2019 (COVID-19) is one of the current global public health threats and vaccination is the most effective tool to reduce the spread and decrease the severity of COVID-19. Diabetes is one of the important chronic diseases threatening human health and is a common comorbidity of COVID-19. There are limited and conflicting data on the interrelationship between diabetes and COVID-19 vaccination. Vaccination may be at risk of worsening glycemia in diabetic patients, and diabetic patients may have a lower immune response after vaccination than the general population, and there is a bidirectional relationship between vaccination and diabetes.

Citation: He YF, Ouyang J, Hu XD, Wu N, Jiang ZG, Bian N, Wang J. Correlation between COVID-19 vaccination and diabetes mellitus: A systematic review. *World J Diabetes* 2023; 14(6): 892-918
URL: https://www.wjgnet.com/1948-9358/full/v14/i6/892.htm
DOI: https://dx.doi.org/10.4239/wjd.v14.i6.892

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic is one of the greatest public health threats to humanity in more than a century. The disease continues to rage across the globe, spanning countries and continents, with severe health, social and economic consequences for the world. COVID-19 is a multifactorial disease that affects nearly all organ systems in the body of the patient. Vaccination is one of the most effective tools to reduce transmission[1] and decrease clinical severity[2]. As of March 16, 2022, more than 10 billion different doses of the COVID-19 vaccine, including boosters, have been administered worldwide[3]. Diabetes mellitus (DM) is a chronic disease that causes high blood glucose levels due to failure of insulin secretion or action[4,5], affecting approximately 537 million adults[6]. DM remains one of the major risk factors for serious illness and worse outcomes in people with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection[7-9]. Many studies have shown that hyperglycemia is associated with an increase in the frequency and severity of any infection, not just COVID-19[10]. This raises concerns about the behavior of the COVID-19 vaccination in diabetic patients and the effects of having been vaccinated and the factors that influence it[11].

Reassuringly, the vaccine has demonstrated efficacy and safety in the prevention of severe COVID-19 in both phase III trials and real-world data[12-14]. The vaccine also plays a key role in protecting vulnerable populations associated with an increased risk of morbidity and mortality, including patients with diabetes[12]. However, there is evidence of multiple immunodeficiencies in patients with DM that affect the innate and acquired immune system[15]. Therefore, it can be expected that the protective effect of vaccination may be weaker compared to the general population. Previous studies have shown reduced immunogenicity to the hepatitis B vaccine in patients with DM, while results are less consistent for influenza, pneumococcal, and varicella zoster[16]. In several recent studies using real-world data,

vaccine efficacy was found to be lower in patients with DM than in the total population[17,18], while another Japanese study reported no significant association between vaccine efficacy and DM[19]. There are conflicting results regarding the immune efficacy of the COVID-19 vaccine in patients with DM. Furthermore, hyperglycemic crisis, acute myocardial injury[20], Guillain-Barre syndrome[21], and herpes zoster[22] are some of the very rare vaccine-related adverse events that have been reported occasionally. In patients with pre-existing DM, does the COVID-19 vaccination cause perturbations in blood glucose levels or even alter the natural history of the disease? There are very limited data on the interrelationship between DM and COVID-19 vaccination.

Therefore it seems important and interesting to understand the interrelationship between COVID-19 vaccination and diabetes. To elucidate this complexity, we summarized almost all current clinical studies and systematically analyzed various factors regarding the interconnection between DM and COVID-19 vaccination in order to inform diabetic patients of the optimal vaccination strategy and clinical management.

MATERIALS AND METHODS

Identify research question

What is the effect of DM on the immunization effect of COVID-19 vaccination? Conversely, does vaccination against COVID-19 disrupt blood glucose? Or accelerate the progression of pre-existing diabetic complications?

Identify relevant types of evidence

An experienced information specialist conducted a comprehensive search of PubMed, MEDLINE, and EMBASE online databases with no time limit, and the last data update was December 2, 2022. We used the keywords "SARS-CoV-2", "COVID-19", "vaccine", "vaccination", "antibody", and "diabetes" individually or in combination to achieve a comprehensive literature search. We also searched the gray literature of medRxiv and bioRxiv as well as the most recent literature of the *Reference Citation Analysis* (https://www.referencecitationanalysis.com). Finally, we manually searched the references cited in the original articles included in the study in order to avoid missing any relevant and important literature. Inclusion criteria were all studies conducted in humans that discussed the relationship between DM and vaccination against COVID-19. Studies that included the same population but reported different data and outcomes were also included. Exclusion criteria were: Non-human (animal), non-English, only exploring willingness to vaccinate, and participants who were not diabetic or who received a vaccine other than the COVID-19 vaccine. The type of diabetes, the type of vaccine, the age of participants, and the type of literature were not restricted. A detailed search strategy is available in the Supplementary Material.

Study selection

After completing the initial search, two independent reviewers conducted a screening process, and literature with quantifiable evidence was included in our review, including case reports, qualitative analyses, and other gray literature. We excluded repetitive publications and articles without relevant data. One reviewer reviewed the selected articles in their entirety, and studies containing full data descriptions were used for data graphs. Any conflicts that arose during the data extraction process were discussed or consulted and resolved by third-party experts. All seven authors were involved in the discussions. Figure 1 shows a visual representation of the inclusion workflow.

Data charting

A total of 2142 publications were retrieved as of December 2, 2022, and after screening by the inclusion criteria described above, we reviewed 208 full-text papers for eligibility, plus three manually retrieved papers, resulting in 54 papers included in this review (Figure 1). We extracted data for each paper regarding the first author's name, country, study design, basic demographic characteristics of participants, the type of vaccination, vaccination regimen, and blood glucose for tabulation and discussion. We did not perform any meta-analysis of the data obtained because, as expected, there was substantial heterogeneity among the designs, methods, populations, and vaccines used in the studies we encountered, making meaningful comparisons between studies impossible. A summary of information on the included studies is presented in Table 1.

RESULTS

A total of 54 studies were included[18,23-75], from 17 countries, including 9 from Japan. The earliest date of the studies was November 2020[48]. There were no randomized controlled studies, but two studies applied propensity score matching (PSM) methods. What was surprising was that one study

Table 1 Characteristics of the included studies

Ref.	Country	Study design	Study time span	Population	Sample size (*n*)	No. of patients with DM (*n*) T1DM	T2DM	Sex (F/M)	Age, median (min-max), yr	Type and name of vaccine	Dose schedule	Related findings
Zhang *et al*[23]	China	Observational study	Between October 2021 and January 2022	The population is aged ≥ 60 yr with hypertension or (/and) DM	1413	620		661/752	67.6	Vero cell (19nCov-CDC-Tan-HB02)	Two doses (day 0, day 28)	After vaccination, there was no significant abnormal fluctuation in blood glucose in diabetic patients
Marfella *et al*[24]	Italy	Prospective observational study	December 2020	Healthcare and educator workers	478		201	212/266	18-60	mRNA-BNT162b2 (Pfizer-BioNTech) or ChAdOx1-S (Astra-Zeneca) or mRNA-1273 (Moderna)	One (day 0, day 21) or two (day 52) doses	Significant decrease in the immune response in people with poorly controlled blood glucose
Kılınç-Toker *et al*[25]	Turkey	Retrospective study	Between August 1, 2021 and October 31, 2021	Hospitalized patients with COVID-19	541	195		282/259	70.2 (21-98)	(CoronaVac) and/or BNT162b2 mRNA (Pfizer-BioNTech)	14 d after dose 2	For hospitalized patients after the second dose, diabetes was not associated with their ICU stay and mortality
Barocci *et al*[26]	Italy	Observational study	Between December 2020 and June 2021	Healthcare workers and university staff	284[5]	8		155/129	43-61	ChAdOx1-S and (BNT162b2/BNT162b2 and ChAdOx1-S/ChAdOx1-S)	2 mo after dose 2	DM does not affect antibody levels
Singh *et al*[27][1]	India	Cross-sectional study	Between January 16, 2021 and May 15, 2021	Healthcare workers	515[4]	0	52	210/305	44.8 ± 13.1[9]	Covishield™ (ChAdOx1-nCOV) or Covaxin™ (BBV-152)	One (day 21) and two (day 21-28, day 83-97, and day 173-187) doses	People with T2DM had a significantly lower seropositivity rate compared to those without
Singh *et al*[28][1]	India	Longitudinal study	Between January 16, 2021 and November 15, 2021	Healthcare workers	481	0	51	195/286	≤ 60 years, *n* = 411; > 60 years, *n* = 70	Covishield™ (ChAdOx1-nCOV) or Covaxin™ (BBV-152)	3 wk, 3 mo, and 6 mo after dose 2	Participants with T2DM have a lower seropositivity rate at all time points
Shim *et al*[29]	Korea	Retrospective study	February2021	Vaccination participants	736	48		433/303	51.5 (20-80)	AZD1222, BNT162b2, mRNA-1273 and Ad26.COV2.S	2 wk before and 6 mo after dose 2	Diabetics had a lower rate of neutralizing antibodies after vaccination
Alqassieh *et al*[30]	Jordan	Prospective observational cohort	Between March and April 2021	Jordanian adults	288	76		189/151	20-60 years, *n* = 137, > 60 years, *n* = 151	Pfizer-BioNTech or Sinopharm	6 wk after dose 2	Although DM negatively affected IgG titer, it was not statistically significant
Wan *et al*[31]	China (Hong Kong)	Population-based study	Between February 23, 2021 and	Patients with T2DM in Hong Kong electronic case records	350963	0	350963	167073/183890	64.7 ± 1.37/68.1 ± 0.74[7]	BNT162b2 or CoronaVac	Complete at least one dose of vaccination	Patients with T2DM do not appear to have higher risks of AESI and acute diabetic

			January 31, 2022								complications after vaccination
Lee *et al*[32]	South Korea	Questionnaire study	Between March 8, 2021 and March 11, 2021	Healthcare workers	1603	27		1261/342	37.7 ± 10.8[9]	ChAdOx1	7 d after dose 1	DM is associated with an increased risk of grade 3 to 4 adverse reactions after the first dose
Rangsrisaeneepitak *et al*[33]	Thailand	PSM observational study	Between June 8, 2021 and July 12, 2021	Healthcare workers and T2DM patients	282		94	129/153	30-83	ChAdOx1 nCoV-19 (AZD1222)	56 d after dose 1	People with T2DM had weaker antibody responses than those without diabetes after the first dose
Sourij *et al*[34]	Austria	Multicentre prospective cohort study	Between April and June 2021	T1DM, T2DM, and healthy participants	150	75	75	68/82	49.2 ± 14.5[9]	BioNTech-Pfizer, Moderna, or AstraZeneca	7 to 14 d after dose 1 and 14 to 21 dafter dose 2	The antibody levels after the second vaccination were comparable in healthy controls and DM patients, irrespective of glycaemic control
Tawinprai *et al*[35]	Thailand	Prospective cohort study	Between March 31, 2021 and May 5, 2021	Healthcare workers	796	11		517/279	40 (30-57)[3]	ChAdOx1 (AZD1222)	At least 21 d after dose 1 and before dose 2	DM reduces the immune response to vaccination
Ali *et al*[18]	Kuwait	Case-control study	August 2021	Non-diabetics and patients with T2DM	262	0	81	126/136	49.3 ± 14.5[9]	BNT162b2 (Pfizer-BioNTech)	At least 3 wk after dose 2	Both neutralizing antibody and IgG antibody titers were significantly lower in the T2DM group than in the non-diabetic group
Karamese *et al*[36]	Turkey	Descriptive study	March 2021	Participants over 65 years of age who have received two doses of vaccine	235	49		111/124	70.4 ± 4.8[9]	CoronaVac	4 wk after dose 1 and 4 wk after dose 2	Lower rates of antibody response were detected in participants with DM
Lustig *et al*[37]	Israel	Single-centre, prospective, longitudinal cohort study	Between December 19, 2020 and January 30, 2021	Health-care workers	2607	139		1883/724	47.7 ± 12.5[9]	Pfizer-BioNTech BNT162b2	1-2 wk after dose 1 and 1-2 wk after dose 2	Decreased antibody response in diabetic patients after vaccination
Islam *et al*[38]	Japan	Cross-sectional study	June 2021	Workers	953	21		654/299	21-75	BNT162b2 (Pfizer-BioNTech)	15 to 71 d after dose 2	Spike IgG antibody titers were lower in the presence of hyperglycemia
Parthymou *et al*[39]	Greece	Longitudinal observational cohort study	September 2021	Healthcare units participants	712	50		444/268	50.8 ± 11.4[9]	BNT162b2 (BioNTech-Pfizer)	3 wk and 3 mo after Dose2	DM is not an independent factor affecting antibody titers
Priddy *et al*[40]	New Zealand	Prospective cohort study	Between June 10, 2021 and September 18, 2021	Participants in two centers	285	28		156/129[6]	52 (16-92)	BNT162b2 (BioNTech-Pfizer)	28 d after dose 2	Participants with diabetes had lower anti-S IgG antibodies compared to those without DM
Naschitz *et al*[41]	Israel	Retrospective	May 2021	Residents in long-term	304	103		208/96	≥ 60	BNT162b2 (Pfizer-	3-4 mo after dose	DM is associated with

		study		geriatric and palliative care and assisted living facilities						BioNTech)	2	negative serological results
Güzel *et al*[42]	Turkey	Prospective study	May 2021[2]	Volunteers, outpatient clinic people, and COVID-19 patients	183	80		98/85	21-60	CoronaVac-SinoVac	21 d after dose 2	IgG antibody levels were significantly lower in patients with DM than in those without DM
Virgilio *et al*[43]	Italy	Multicenter prospective study	Between June 2021 and December 2021	Residents of long-term care facilities	555	0	140	378/177	82.1	BNT162b2 (Cominarty) Moderna (mRNA-1273)	Before the vaccination, 2 mo, and 6 mo after dose 1	Vaccination in elderly residents with T2DM is associated with a reduced humoral immune response
Patalon *et al*[44]	Israel	Retrospective cohort study	Between February and May 2021	A large patient cohort from Maccabi Healthcare Services	4740	377		1914/2826	16-59 years, n = 3355; ≥ 60 years, n = 1385	BNT162b2 (BioNTech-Pfizer)	Two vaccinations at intervals of 21 to 27 d	DM is not a relevant factor affecting antibody levels
Mitsunaga *et al*[45]	Japan	Prospective study	Between April 15, 2021 and June 9, 2021	Hospital's workers	374	6		264/110	36	BNT162b2 vaccine (COMIRNATY (Tozinameran)	Before vaccination, 7 to 20 d after dose 1, and 7 to 20 d after dose 2	HbA1c higher than 6.5% was a significant suppressor of antibody responses
Papadokostaki *et al* [46]	Greece	Prospective observational study	Between May and September 2021.	Participants attended the vaccination center	174	14	44	107/67	52.6 ± 10.6	BNT162b2 (BioNTech-Pfizer)	21 d after dose 1, 7-15 d after dose 2, and 70-75 d after dose 2 but before dose 3	It was high and similar after the second dose in both participants with and without DM
Zhao *et al*[47]	United States	Prospective longitudinal study	Between December 2020 and December 2021	Veterans and healthcare workers	124	39		33/91	20-95	BNT162b2 (Pfizer-BioNTech)	48 h before dose 1 and dose 2, 1 mo, 3 mo, 6 mo, 12 mo after dose 2, and 1 mo after dose 3	DM was significantly associated with a decrease in response intensity after completion of the primary vaccine series, but responses to the third dose were generally robust
Santotoribio *et al* [48]	Spain	Descriptive, retrospective, observational, and cross-sectional study	Between November 1, 2020 and March 31, 2021	Infected patients and vaccinated subjects	175	17		112/63	51.0 (19-89)	Pfizer-BioNTech	At least 21 d after dose 2	Serum antibody levels did not decrease significantly in patients with DM
Mehta *et al*[49]	India	Observational cohort study	Between March 2021 and October 2021	Vaccinated patients with AIRDs	495	63		416/79	56.5	AZD1222 (AstraZeneca)	4 wk and10-14 wk after dose 2	DM was significantly associated with lower anti-RBD antibodies
Ajlan *et al*[50]	Saudi Arabia	PSM prospective study	June 14, 2022[2]	Patients from a large hospital	431	191		136/295	51.3 ± 16.2[9]	BNT162b2 or ChAdOx1	7 d after dose 1 and dose 2, and 2 wk after dose 1 and dose 2	There was no difference in the primary outcome between the two vaccine platforms. Unrespons-

											iveness was mainly linked to DM
Billany *et al*[51]	United Kingdom	Prospective observational study	March 2021	Maintenance hemodialysis patients	94	43		38/56	62.1 ± 12.2[9]	BNT162b2 or AZD1222	28 d after dose 1	There was no difference in antibody testing with or without DM
Aberer *et al*[52]	Austria	Multicenter prospective study	Between April and June 2021	DM patients	74	58	16	NR	T1DM: 39.5 ± 14.1; T2DM: 60.6 ± 6.2	BioNTech-Pfizer and Moderna and AstraZeneca	First dose	No change in insulin dose before and after vaccination. Vaccination significantly reduced TIR in T1DM patients, but had no effect on TIR in T2DM patients
Piccini *et al*[53]	Italy	Observational cohort study	Between March and June 2021	T1DM patients	39	39	0	17/22	18.7 ± 2.1[9]	mRNA-BNT162b1 (Pfizer-BioNTech) and Moderna (mRNA-1273)	One (day 7, day 14) and two (day 7, day 14) doses and 14 d after dose 1 and dose 2	COVID-19 vaccination was safe and not associated with significant perturbation of glycemic control in patients with T1DM
Heald *et al*[54][1]	United Kingdom	Observational cohort study	Between January 14, and March 7, 2021	T1DM patients	20	20	0	11/9	53 (26-70)	mRNA-BNT162b2 (Pfizer-BioNTech) and Oxford /AstraZeneca	7 d before and 7 d after dose 1	COVID-19 vaccination can cause temporary relative hyperglycemia in people with T1DM. No relationship between vaccine type and blood glucose perturbation
D'Onofrio *et al*[55]	Italy	Observational cohort study	July 13, 2021[2]	T1DM (AD) patients	35	35		14/21	36 (27-51)[3]	mRNA-BNT162b2 (Comirnaty)	14 d before and 3 d after dose 1 and dose 2	No significant differences in TIR, TAR, TBR, and CV between, after, and before the COVID-19 vaccination in T1DM patients
Heald *et al*[56][1]	United Kingdom	Survey and evaluation study	Between January 5, 2021 and April 4, 2021	Adults (18 years of age or more) with T1DM	97	97	0	51/46	44 (18-70)	Pfizer-BioNTech or Oxford-AstraZeneca	7 d before and 7 dafter dose 1	In T1DM, vaccination can cause a temporary perturbation of interstitial glucose. There is no difference between vaccines
Gouda *et al*[57]	Greece	Observational study	March 2022	T1DM patients	135[8]	135	0	72/63	11.7 (5-18)	BNT162b2 (Pfizer-BioNTech), Moderna (mRNA-1273), or AstraZeneca	7 d before and 7 d after dose 1, dose 2, and dose 3	SARS-CoV-2 vaccination in children and adolescents with T1DM is safe and is not associated with immediate glucose imbalance
Sakurai *et al*[58]	Japan	Case report	December 11, 2021[2]	Healthy woman	1			1/0	36	mRNA-BNT162b2 (Pfizer-BioNTech)	First dose	mRNA vaccine is associated with new-onset T1DM
Patrizio *et al*[59]	Italy	Case report	September 15, 2021[2]	T2DM patient	1	0	1	0/1	52	mRNA-BNT162b2 (Pfizer-BioNTech)	Second dose	T1DM may be triggered after SARS-CoV-2

											vaccination
Aydoğan *et al*[60]	Turkey	Case series	Between May 2021 and October 2021	One had Hashimoto's thyroiditis, and the other 3 were healthy	4			1/3	27-56	mRNA-BNT162b2 (Pfizer-BioNTech) or CoronaVac	Second dose	Vaccination with BNT162b2 may trigger T1DM
Sato *et al*[61]	Japan	Case report	April 19, 2022[2]	Malignant melanoma patient	1			0/1	43	mRNA-based SARS-CoV-2 vaccination	Second dose	mRNA vaccine may trigger T1DM
Yakou *et al*[62]	Japan	Case series	December 21, 2021[2]	T1DM patients	2	2	0	2/0	52-71	mRNA-BNT162b2 (Pfizer-BioNTech)	Second dose	A temporary decrease in insulin secretion after vaccination
Mishra *et al*[63]	India	Case series	Between January 18, 2021 and March 4, 2021	T2DM patients	3	0	3	1/2	58-65	Covishield™ (ChAdOx1-nCOV) (AstraZeneca)	First dose	Vaccination may result in a mild and temporary increase in blood glucose levels
Abu-Rumaileh *et al*[64]	Jordan	Case report	January 14, 2021	Hypertension patient	1			0/1	58	mRNA-BNT162b1 (Pfizer-BioNTech)	Second dose	COVID-19 vaccine has a risk of causing new-onset T2DM
Sasaki *et al*[65]	Japan	Case report	December 13, 2021[2]	Osteoporosis, mild glucose intolerance	1	0	0	1/0	73	Moderna (Spikevax, mRNA-1273)	Second dose	The development of T1DM is attributable to the COVID-19 vaccination
Lee *et al*[66]	United States	Case Series	June 30, 2021[2]	T2DM and hypertension patients	3	0	2	1/2	52-87	mRNA-BNT162b1 (Pfizer-BioNTech) and Moderna (Spikevax, mRNA-1273)	First dose	Vaccination may trigger a hyperglycemic episode and DKA
Edwards *et al*[67]	United Kingdom	Case Series	April 2021	Hypertension, hypothyroidism, and pre-diabetes	3			0/3	53-68	Covishield™ (ChAdOx1-nCOV)	First dose	The first administration of the COVID-19 vaccine can trigger an acute hyperglycemic crisis
Ganakumar *et al*[68]	India	Case series	November 2021	T1DM	2	2	0	1/1	20-25	COVISHIELD (ChAdOx1 nCoV-19) or COVAXIN (BBV152)	1 to 4 d after dose 2	COVID-19 Vaccination has the potential to induce DKA
Zilbermint *et al*[69]	United States	Case report	September 11, 2021[2]	T1DM	1	1	0	1/0	24	Moderna (mRNA-1273)	15 h after dose 2	A plausible mechanism exists between COVID-19 vaccination and DKA
Yaturu *et al*[70]	United States	Case report	May 2021	Hypertension, primary hyperparathyroidism, and obesity patient	1	0	1	0/1	56	BNT162b2 (Pfizer-BioNTech)	Right after the second dose	COVID-19 Vaccination has the potential to induce HHS
Kshetree *et al*[71]	United States	Case report	NR	Hypertension and pre-diabetes	1	1	0	0/1	69	mRNA vaccine	2 mo after dose 3	COVID-19 mRNA vaccine has the potential to induce DKA
Prasad[72]	India	Case report	March 2021	Patient with T2DM	1	0	1	1/0	73	Covishield	6 d after dose 1	Vaccination may cause glycaemic disturbances

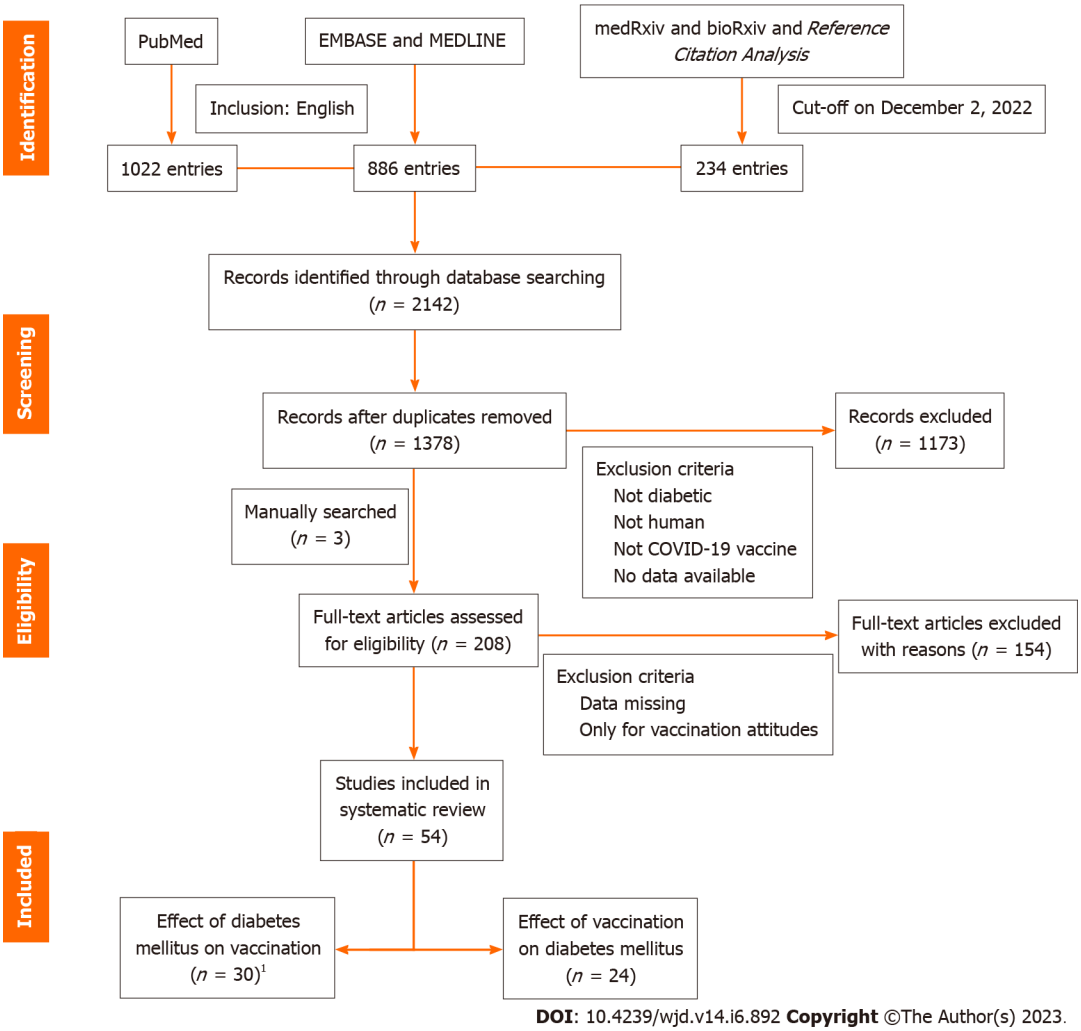
Sasaki *et al*[73]	Japan	Case report	January 4, 2022[2]	Healthy person	1	1	0	1/0	45	BNT162b2 (Pfizer-BioNTech)	1 d after dose 1	COVID-19 vaccine might trigger the onset of fulminant T1DM in susceptible individuals
Yano *et al*[74]	Japan	Case report	November 11, 2021[2]	Healthy person	1	1	0	1/0	51	Moderna (mRNA-1273)	28 d after dose 1	COVID-19 vaccination can induce T1DM in some individuals
Ohuchi *et al*[75]	Japan	Case report	November 2021[2]	Cutaneous malignant melanoma with axillary lymph node metastasis	1	1	0	0/1	45	BNT162b2 (Pfizer-BioNTech)	3 d after dose 2	There is a highly suspicious causal relationship between fulminant T1DM and COVID-19 vaccination

[1]The authors are the same, but the individual studies are different, including different phases, different samples, and different data.
[2]Take the date of receipt of the manuscript.
[3]Median (25^{th}-75^{th} percentile).
[4]Sample size for completing the second dose.
[5]Sample size for fully completed questionnaires.
[6]Contains a Non-binary participant.
[7]Age (mean ± SD) is divided according to BNT162b2 and CoronaVac groups.
[8]Sample size for T1DM, of which 70 received at least one dose of the vaccine and the other 65 were unvaccinated.
[9]mean ± SD.
NA: Not available; NR: Not reported; COVID-19: Coronavirus disease 2019; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; PSM: Propensity score matching; HbA1c: Glycated hemoglobin; TIR: Time in range; DM: Diabetes mellitus; T1DM: Type 1 diabetes mellitus; T2DM: Type 2 diabetes mellitus; HHS: Hyperosmolar hyperglycemic syndrome; DKA: Diabetic ketoacidosis; AD: Autoimmune diabetes; AIRDs: Autoimmune Rheumatic Diseases; AESI: Adverse events of special interest; F: Female; M: Male; ICU: Intensive care unit; TAR: Time above range; TBR: Time below range; CV: Coefficient variation.

analyzed the bidirectional relationship between vaccination and blood glucose[23]. There were 30 studies that discussed the effect of diabetes on vaccination[18,23-51], two of which were specifically about whether DM increased adverse effects after vaccination[31,32], and three of which had participants with autoimmune rheumatic disease[49], organ transplantation[50], and a special group on blood pressure dialysis[51]. The other 24 studies were on the effect of vaccination on DM[52-75] and included 18 case reports or case series[58-75]. The largest sample size was 350,963, a population-based study from Hong Kong, China, which evaluated the risk of adverse events of special concern and acute diabetic complications after COVID-19 vaccination in the type 2 DM (T2DM) population[31]. Of the sample included in the 54 studies, the youngest age was five years[57] and the oldest was 98 years[25]. Only one study analyzed the effects of glycemia on both cellular and humoral responses after vaccination[24]. Only one study performed a comparative analysis between type 1 diabetes and type 2 diabetes[34]. The authors of some studies claim that they are reporting for the first time, trying to fill a gap in the literature regarding certain relationships between COVID-19 vaccination and DM.

Results on the effect of vaccination on DM

From the current studies, the effect of vaccination on diabetes is mainly manifested in the effect on blood glucose after vaccination, with a total of 24 studies describing this relationship, including 18 case reports or case series. To make the various characteristics of these case series readily apparent, we have



DOI: 10.4239/wjd.v14.i6.892

Figure 1 Flow diagram of literature search. [1]One study analyzed the bidirectional relationship between vaccination and blood glucose. COVID-19: Coronavirus disease 2019.

additionally tabulated a total of 29 cases from these 18 case reports or case series (Table 2). Of these 29 cases, 12 were new-onset type 1 DM (T1DM) and three were new-onset T2DM. Fourteen cases were vaccinated with two doses, 14 with only one dose, and one with a third dose. mRNA vaccines were used in 19 cases (13 cases of mRNA-BNT162b2 (Pfizer-BioNTech) and 6 cases of Moderna (mRNA- 1273)) and eight cases used the adenoviral vector vaccine Covishield™ (ChAdOx1-nCOV or AstraZeneca). Most events occurred within days of vaccination, with the longest being a diagnosis of new-onset T1DM two months after the third dose[71]. No deaths were reported. Of these 24 studies, only three indicated that vaccination had no effect on blood glucose[53,55,57], while the rest indicated that it may cause an increase in blood glucose. No vaccinated individuals with episodes of hypoglycemia were identified. Of course, it cannot be ruled out that some patients develop mild or self-limiting hypoglycemia after vaccination, which may not cause certain subjective symptoms in patients and therefore may go undocumented by clinical diagnosis.

Results on the effect of DM on vaccination

Of the 30 studies on the effect of DM on vaccination, only one study analyzed the correlation between blood glucose levels and the humoral and cellular immunity of the organism after immunization[24]. Most of the studies examined whether blood glucose levels as an indicator of effect or DM as comorbidity negatively affected the immune response to vaccination. Twenty-one of the studies showed that DM reduced response to vaccination, while the other nine indicated that DM had no effect on vaccine efficiency[23,25,26,30,34,44,46,48,51]. Some studies also quantified the association with vaccine biological effects in terms of patient-specific attributes. Fifteen studies expressed a negative correlation between age and immune response, with older individuals having a weaker immune response than their younger individuals[25,28-30,32-34,36,37,40,42,45,47,51]. Seven studies showed a correlation between gender and immune response after vaccination, with women having a more positive immune effect than men[25,27,32,33,35,39,44]. Eight studies analyzed the effect of vaccine type on the immune

Table 2 Summary of the case report or case series about the effect of SARS-CoV-2 vaccination on blood glucose

Ref.	Age (yr)	Gender	Type and name of vaccine	Blood glucose (mg/dL)/HbA1c (%) pre-vaccination	Blood glucose (mg/dL)/HbA1c (%) post-vaccination	Onset after vaccination	Pre-existing condition	Final diagnosis	C-peptide (ng/mL)	GAD65Ab (IU/mL)	Treatment	Outcomes	Conclusion
Sakurai *et al* [58]	36	Female	mRNA-BNT162b2 (Pfizer-BioNTech)	Normal	501/7.0	3 d after dose 1	None	Fulminant T1DM	0.13	NA	Insulin infusion	Discharged	mRNA vaccine is associated with new-onset T1DM
Patrizio *et al* [59]	52	Male	mRNA-BNT162b2 (Pfizer-BioNTech)	53[1]	87[1]	4 wk after dose 2	Vitiligo vulgaris and T2DM	Graves' disease and T1DM	1	61.2	Insulin analogues	NR	T1DM may be triggered after SARS-CoV-2 vaccination
Aydoğan *et al*[60]	56	Male	mRNA-BNT162b1 (Pfizer-BioNTech)	Normal	440/8.2	15 d after dose 2	Vitiligo vulgaris and Hashimoto's thyroiditis	T1DM	1.5	> 2000	Insulin infusion	Recovery	Vaccination with BNT162b2 may trigger T1DM
	48	Male	mRNA-BNT162b2 (Pfizer-BioNTech)	Normal	352/10.1	8 wk after dose 2	None	T1DM	0.97	94	Low-carbohydrate diet	Recovery	
	27	Male	mRNA-BNT162b2 (Pfizer-BioNTech)	Normal	320/12.5	3 wk after dose 2	None	T1DM	0.87	725	Basal insulin	Recovery	
	36	Male	mRNA-BNT162b2 (Pfizer-BioNTech) and CoronaVac	Normal	526/12.6	3 wk after dose 2	None	T1DM	0.38	234	Insulin infusion	Recovery	
Sato *et al*[61]	43	Male	mRNA-based SARS-CoV-2 vaccination	94/5.6	655/8.0	14 d after dose 2	Malignant melanoma	Fulminant T1DM	0.33		Insulin infusion	Discharged	mRNA vaccine may trigger T1DM
Yakou *et al* [62]	71	Female	mRNA-BNT162b1 (Pfizer-BioNTech)	93/8.1	944/8.0	1 d after dose 2	T1DM	Diabetic ketoacidosis	< 0.03	> 2000	Insulin infusion	Discharged	Risk of inducing ketoacidosis after vaccination in T1DM patients
	52	Female	mRNA-BNT162b1 (Pfizer-BioNTech)	106	494/11.6	1 d after dose 2	T1DM	Diabetic ketoacidosis	ND	123	Insulin infusion	Discharged	
Mishra *et al* [63]	58	Female	Covishield™ (ChAdOx1-nCOV) (AstraZeneca)	110	183	1 d after dose 1	T2DM	T2DM	NR	NR	Increased dose of metformin.	Discharged	Vaccination may result in a mild and temporary increase in blood glucose levels
	64	Male	Covishield™ (ChAdOx1-nCOV) (AstraZeneca)	95	150	1 d after dose 1	T2DM	T2DM	NR	NR	Without additional intervention	Discharged	
	65	Male	Covishield™ (ChAdOx1-nCOV) (AstraZeneca)	107	186	6 d after dose 1	T2DM	T2DM	NR	NR	Without additional intervention	Discharged	
Abu-Rumaileh *et al*[64]	58	Male	mRNA-BNT162b1 (Pfizer-BioNTech)	80	1253/13	26 d after dose 1	Hypertension	T2DM	1.1	NR	Insulin infusion	Discharged	COVID-19 vaccine has a risk of causing new-onset T2DM

Sasaki *et al* [65]	73	Female	Moderna (Spikevax, mRNA-1273)	7.3	318/9.3	8 wk after dose 2	Osteoporosis, mild glucose intolerance	T1DM	0.48	> 2000	Intensive insulin therapy	NR	COVID-19 Vaccination may lead to the new-onset T1DM
Lee *et al*[66]	52	Female	mRNA-BNT162b2 (Pfizer-BioNTech)	5.5-6.2	1062/12.0	3 d after dose 1	Hypertension	T2DM and nonketotic HHS	NR	NR	Insulin infusion.	Discharged	Vaccination may trigger HHS
	60	Male	Moderna (mRNA-1273)	7.5	847/13.2	2 d after dose 1	T2DM	T2DM and HHS	NR	NR	Insulin infusion	Discharged	Vaccination may trigger a hyperglycemic episode
	87	Male	Moderna (mRNA-1273)	7	923	10 d after dose 1	T2DM	T2DM and HHS and DKA	NR	NR	Insulin infusion	Discharged	Vaccination may trigger HHS and DKA
Edwards *et al*[67]	59	Male	Covishield™ (ChAdOx1-nCOV)	5.6	594/14.1	21 d after dose 1	Obesity	Hyperglycemic ketosis	235[2]	NR	NA	Discharged	The first administration of the adenovirus-vectored COVID-19 vaccine can trigger an acute hyperglycemic crisis
	68	Male	Covishield™ (ChAdOx1-nCOV)	6.5	918/14.7	36 d after dose 1	Pre-diabetes	Mixed HHS/DKA	561[2]	NR	ICU admission	Discharged	
	53	Male	Covishield™ (ChAdOx1-nCOV)	6.2	576/17.1	20 d after dose 1	Pre-diabetes	DKA	377[2]	NR	ICU admission	Discharged	
Ganakumar *et al*[68]	20	Male	COVISHIELD (ChAdOx1 nCoV-19)	NR	14.1	1 d after dose 2.	None	Severe DKA	NR	NR	Insulin infusion	Discharged	COVID-19 vaccination has the potential to induce DKA
	25	Female	COVAXIN (BBV152)	NR	16.3	4 d after dose 2	None	Severe DKA	NR	NR	Insulin infusion	Discharged	
Zilbermint *et al*[69]	24	Female	Moderna (mRNA-1273)	NR	505/12.0	15 h after dose 2	T1DM	Severe DKA	NR	NR	Insulin infusion	NR	A plausible mechanism exists between COVID-19 vaccination and DKA
Yaturu *et al* [70]	56	Male	BNT162b2 (Pfizer-BioNTech)	5.6	997/14	Right after the second dose.	Hypertension, primary hyperparathyroidism, and obesity	T2DM and HHS	NR	NR	Insulin infusion	Discharged	COVID-19 vaccination has the potential to induce HHS
Kshetree *et al* [71]	69	Male	mRNA vaccine	5.8	13.7	Two months after dose 3	Hypertension and pre-diabetes	T1DM and DKA	0.4	0.33	Insulin infusion	Discharged	COVID-19 mRNA vaccine has the potential to induce DKA
Prasad[72]	73	Male	Covishield	92/7.1	215/8	6 d after dose 1	T2DM	T2DM	NR	NR	Insulin infusion	Discharged	Vaccination may cause glycaemic disturbances
Sasaki *et al* [73]	45	Female	BNT162b2 (Pfizer-BioNTech)	Normal	344/7.6	1 d after dose 1	None	Fulminant T1DM and DKA	NR	NA	Insulin infusion	Discharged	COVID-19 vaccine might trigger the onset of fulminant T1DM in susceptible individuals
Yano *et al*[74]	51	Female	Moderna (mRNA-1273)	Normal	648/10.3	28 d after dose 1	None	Fulminant T1DM and DKA	1.72	NA	Insulin infusion	Discharged	COVID-19 vaccination can induce T1DM in some individuals
Ohuchi *et al*	45	Male	BNT162b2 (Pfizer-	NR	655	3 d after dose	Cutaneous malignant	Fulminant	0.99	Negative	NR	NR	There is a highly suspicious

[75]	BioNTech)	2	melanoma	T1DM	causal relationship between fulminant T1DM and vaccination, especially in patients treated with ICI

[1]Unit: mmol/mol and reference range is 20-38.
[2]Unit: pmol/L and the reference range is 370-1470.
NA: Not available; ND: Not detected; NR: Not reported; COVID-19: Coronavirus disease2019; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; HbA1c: Glycated hemoglobin; DM: Diabetes mellitus; T1DM: Type 1 diabetes mellitus; T2DM: Type 2 diabetes mellitus; HHS: Hyperosmolar hyperglycemic syndrome; DKA: Diabetic ketoacidosis; ICI: Immune checkpoint inhibitors.

response after vaccination in patients with DM, and four of these studies showed an effect[26,27,30,50]. There were also studies that concluded that mixed or heterologous vaccination produced better vaccine efficiency[25,26]. Three studies suggested that participants with previous SARS-CoV-2 infection would have a better antibody response than SARS-CoV-2-naive individuals[28,47,51]. We attempted to systematize the variables in the literature regarding the interrelationship between diabetes and vaccination and summarized the important findings of the studies related to these variables in Table 3. Ten studies mentioned adverse effects of vaccination[23,26-29,33-35,50,53] and only one study manifested that it would have an effect on antibody production[29]. Regarding the effect of BMI on vaccination, one study stated that a lower BMI increased the risk of grade 3 to 4 adverse reactions compared to normal-weight individuals[32], while another study showed that a higher BMI decreased the immune response after vaccination[42].

Results for "no effect"

Of the 54 studies included, a total of 12 studies indicated a "no effect" relationship between DM and vaccination. Nine of them concluded that DM had no effect on the immune response to the vaccine[23,25,26,30,34,44,46,48,51]. Similarly, three studies showed no effect of vaccination on DM or blood glucose [53,55,57]. Of the two studies that specifically investigated DM and adverse reactions to vaccination[31,32], one suggested that patients with T2DM did not appear to have a higher risk of adverse reactions after vaccination[31].

DISCUSSION

Effect of the COVID-19 vaccination on DM

Does COVID-19 vaccination lead to dysglycemia or even a hyperglycemic crisis with serious adverse consequences in patients? Of the 54 studies included, most suggested that there may be some association between vaccination and blood glucose, mainly in the form of elevated blood glucose or even induction of new-onset DM. Table 2 Lists 12 cases of new-onset DM. In addition, Heald *et al*[54] also implied that COVID-19 vaccination can cause temporary relative hyperglycemia in patients with T1DM. SARS-CoV-2 infection is known to cause an immune stress response and dysglycemia. The worsening of blood glucose that occurs after vaccination is thought to have a possible common pathophysiology with the hyperglycemia associated with SARS-CoV-2 infection. Possible mechanisms

Table 3 Outcomes of the studies based on the association between vaccination and diabetes

Ref.	Assessed variables	Findings related to variables	Conclusion	Limitations
Zhang *et al*[23]	Hypertension, Comorbidity, Side effects	None	After vaccination, no significant abnormal fluctuations in blood glucose values were observed in the DM patients	Lack of data on the duration of antibodies after vaccination in the study population
Marfella *et al*[24]	HbA1c, Time since vaccination, type of vaccine	On Day 21 after the second vaccine dose, T2DM patients with HbA1c > 7% showed significantly reduced virus-neutralizing antibody capacity than normoglycemic subjects and T2DM patients with good glycaemic control. At 21 d after the first vaccine dose, neutralizing antibody titers and CD4 cytokine responses involving type 1 helper T cells were lower in T2DM patients with HbA1c levels > 7% than in individuals with HbA1c levels ≤ 7%. The reduction of HbA1c levels 52 d after vaccination was associated with neutralizing antibody titers and CD4 cytokine increases	Hyperglycemia at the time of vaccination can worsen the immune response, and proper glycemic control can improve the immune response	The statistical significance of the relevant indicators was relatively low
Kılınç-Toker *et al*[25]	Age, sex, mixed vaccination, delta variant, BMI, Diabetes, hypertension, COPD, cardiovascular diseases, chronic kidney disease, cancer	Age, male gender, delta variant, and mixed vaccination (CoronaVac plus BioNTech) were associated with death. The delta variant had higher ICU admission and mortality rate	For hospitalized patients who received two doses of the vaccine, diabetes was not associated with their ICU stay and mortality	Retrospective design, short follow-up, and assessment of inpatients only
Barocci *et al*[26]	Homologous vaccination, heterologous vaccination, type of vaccine, vaccine schedule, sex, age, BMI, smoking, DM, cardiovascular diseases, respiratory tract diseases, previous SARS-CoV-2 infection, side effects	Heterologous vaccination induced a significantly higher humoral response than homologous vaccination. The type of vaccine influenced antibody titers	DM does not affect antibody levels	Results were influenced by anti-S IgG levels in asymptomatic subjects
Singh *et al*[27][1]	Sex, T2DM, age, BMI, side effects, type of vaccine, dose 1, dose 2	Gender, presence of comorbidities, and vaccine type were independent predictors of antibody seropositivity and anti-spike antibody titer levels. Patients with T2DM had a significantly lower seropositivity rate compared to those without the comorbid disease. Seropositivity rates were lower in those with T2DM compared to those without T2DM. Both vaccine recipients had similar mild to moderate adverse events, and none had serious side effects	T2DM is associated with lower seropositivity rates and anti-spike antibody titers	No assessment of the cell-mediated immune response
Singh *et al*[28][1]	Age, previous SARS-CoV-2 infection, sex, BMI, side effects, type of vaccine, dose 1, dose 2, T2DM, blood group, dyslipidemia, ischemic heart disease	The seropositivity rate was significantly higher in the ≤ 60 years age group than in the > 60 years age group at all time points. GMT was significantly higher in participants with past SARS-CoV-2 infection than in SARS-CoV-2-naiveindividuals.	Participants with T2DM had a lower rate of seropositivity at all time points	The sample was drawn from a healthy population with few comorbidities
Shim *et al*[29]	Age, DM, type of vaccine, side effects, vaccination interval, hypertension, BMI, sex	There were significant differences in general and neutralizing antibodies based on age, vaccine type, vaccination interval, pain score, diabetes, and hypertension	For all vaccines, subjects with diabetes showed lower rates of neutralizing antibody production after vaccination	Vaccination priority policies bring heterogeneity across age groups
Alqassieh *et al*[30]	Age, type of vaccine, hypertension, cardiovascular disease, DM, sex, BMI	Old people (> 60) had lower IgG titers than their younger counterparts. The use of the Pfizer-Biotech vaccine was positively associated with positive IgG titers, while cardiovascular disease had a negative effect on IgG titers. Although diabetes had a negative impact on positive IgG titers, it was not statistically significant	Although DM negatively affected IgG titer positivity, it was not statistically significant	Samples were collected only once at a specific period (6 wk) after vaccination
Wan *et al*[31]	Dose 1, dose 2, HbA1c, side effects	None	Patients with T2DM do not appear to have higher risks of AESI and acute diabetic complications after vaccination	Adverse events are defined using diagnosis codes and may be biased by underdiagnosis or misclassification

Lee *et al*[32]	Sex, age, DM, type of vaccine, BMI	Being young, female or underweight, and having diabetes were associated with an increased risk of developing grade 3 to 4 adverse reactions after the first dose of the ChAdOx1nCoV-19 vaccine	DM is associated with an increased risk of grade 3 to 4 adverse reactions after the first dose of vaccine, especially in women	Sample from relatively healthy subjects working in hospitals
Rangsrisaeneepitak *et al*[33]	T2DM, age, sex, BMI, side effects	After the first dose of AZD1222, the antibody response was weaker in T2DM patients than in non-diabetic patients. The seroconversion rate was higher in the control group than in the diabetic group. Older age was associated with a weaker antibody response in older diabetic patients. The GMC of SARS-CoV-2 IgG antibodies at 56 d was significantly lower in diabetic patients than in age- and sex-matched controls. In the age- and sex-matched controls, SARS-CoV-2 IgG antibody levels were significantly higher in women than in men. During the first 24 h, injection site reactions were more common in diabetic patients than in healthy controls	After the first dose of AZD1222, the antibody response was weaker in T2DM patients than in non-diabetic patients	Participants in the control group were healthcare workers, so natural immunity may have been a confounding factor
Sourij *et al*[34]	T2DM, eGFR, HbA1c, side effects, T1D	Age and renal function were significantly associated with the extent of antibody levels. The most common side effect was injection site reactions, with a significantly lower rate in patients with T2DM	The antibody levels after the second vaccination were comparable in healthy controls and in DM patients, irrespective of glycaemic control	Focused only on the humoral immune response after vaccination, but did not investigate the cellular immune response
Tawinprai *et al*[35]	DM, hematologic disease, sex, age, time since the first dose of vaccination, BMI, side effects, cardiovascular disease, hypertension, dyslipidemia, end-stage kidney disease	Participants with diabetes or hematologic comorbidities had lower concentrations of anti-RBD antibodies. Anti-RBD antibody concentrations were significantly higher in female participants than in male participants. The immune response was lower in older participants. Anti-RBD antibody concentrations were significantly higher at 2 and 3 mo post-vaccination than at 1-mo post-vaccination	Participants with diabetes or hematologic comorbidities had lower concentrations of anti-RBD antibodies	The presence of participants who did not complete two anti-RBD antibody assays withdrew from the study
Ali *et al*[18]	T2DM, age, sex, BMI, comorbidity, previous SARS-CoV-2 infection, hypertension	T2DM is associated with lower titers of neutralizing and IgG antibodies	Both neutralizing antibody and IgG antibody titers were significantly lower in the T2DM group than in the non-diabetic group	Participants in the study were self-selected verbally and through job advertisements
Karamese *et al*[36]	T2DM, age, hypertension, COPD, dose 1, dose 2	Lower antibody response rates were detected in participants with T2DM and in those aged 65 years and older	DM patients have lower antibody levels	The study population was an advanced age group with a high number of comorbidities
Lustig *et al*[37]	Age, sex, DM, immunosuppression, hypertension, heart disease, autoimmune disorders, BMI	Lower antibody concentrations are consistently associated with males, older age, immunosuppression, diabetes, hypertension, heart disease, and autoimmune disorders	Lower IgG concentrations and lower detectable IgA antibodies were observed in DM patients, indicating a reduced antibody response to vaccination in these patients	The sample was drawn from a healthy population with few comorbidities
Islam *et al*[38]	Hyperglycemia, FPG, age, sex, BMI, hypertension, smoking, alcohol consumption	Spike IgG antibody titers were lower in the presence of hyperglycemia and IFG	Vaccine recipients with diabetes and IFG had lower concentrations of SARS-CoV-2 spike IgG antibodies than the vaccine recipients with normoglycemia did	Associations observed in cross-sectional studies do not necessarily indicate causality
Parthymou *et al*[39]	Sex, age, smoking, BMI, DM, hypertension, statin use, vitamin D levels	Age, male gender, and tobacco use are negatively associated with antibody titers after COVID-19 vaccination	Antibody titers were numerically lower in diabetic patients, but this association was not statistically significant	Reliance on questionnaires to record anthropometric parameters and medical history affects reliability
Priddy *et al*[40]	Age, DM, sex, BMI, race	IgG and neutralization responses decreased with age. Lower responses were associated with age ≥ 75 and DM	Lower responses were associated with DM	Most of the IgG and neutralization tests used are not standardized
Naschitz *et al*[41]	Cancer, DM, congestive heart failure, sex, age,	Cancer, DM, or congestive heart failure were all associated with having a negative serology	DM is associated with negative serological	There was a large age difference between the

	hypertension, COPD, cerebrovascular disease, chronic liver disease, cognitive disability	result	results	two sample groups
Güzel *et al*[42]	Cardiovascular diseases, DM, age, BMI, sex, smoking, vitamin use, viral load, comorbidities	Cardiovascular disease and diabetes were associated with lower IgG antibody levels. In the healthcare workers group, IgG antibody response values were negatively correlated with BMI and age	IgG antibody levels were significantly lower in patients with DM than in those without DM	ELISA test may lead to false positive results
Virgilio *et al*[43]	Sex, T2DM, insulin therapy	The negative impact of diabetes in determining a steeper antibody decline was greater in female residents than in male residents. T2DM is associated with a reduced humoral immune response after SARS-CoV-2 vaccination. Antibody kinetics in diabetic patients receiving insulin therapy are similar to those in patients without diabetes	Vaccination in elderly residents with type 2 diabetes is associated with a reduced humoral immune response	Data on blood glucose or glycated hemoglobin levels were not specifically collected to assess the control or severity of diabetes
Patalon *et al*[44]	Sex, age, BMI, COPD, DM, congestive heart failure, inflammatory bowel disease	Females were associated with higher levels of antibodies. Lower antibody levels were observed in higher age groups	DM is not a relevant factor affecting antibody levels	The study population was older and had more comorbidities
Mitsunaga *et al*[45]	Age, Hypertension, HbA1c, Outdoor exercises, Vaccination interval, BMI, COPD, Dyslipidemia, DM, Autoimmune diseases, Cancer, dose 1, dose 2, BG	Older than 60 years, hypertension, HbA1c higher than 6.5%, and lack of outdoor exercises were significant suppressors of antibody responses, whereas the length of days from the first to the second vaccination longer than 25 d promoted a significant antibody response	HbA1c higher than 6.5% was a significant suppressor of antibody responses	The sample was relatively healthy health workers but did not include participants with serious comorbidities
Papadokostaki *et al*[46]	Age, DM, dose 1, dose 2, sample testing time, HbA1c, BMI, duration of diabetes, HbA1c	In the diabetic group, Abs-RBD-IgG was significantly correlated with age and time, and dose after vaccination	The humoral immune responses after the second dose were high and similar in participants with and without DM	No comparison between type 1 and type 2 diabetes
Zhao *et al*[47]	DM, dose 1, dose 2, dose 3, age, end-stage kidney disease, cancer, steroid use, previous SARS-CoV-2 infection, time since vaccination	DM was significantly associated with a decrease in response intensity after completion of the primary vaccine series, but responses to the third dose were generally robust. Age and malignancy had a negative effect on the initial strength of the humoral immune response. Being over 65 years, end-stage renal disease, diabetes, and clinical comorbidities of steroid use had a negative effect on the humoral immune response. SARS-CoV-2 infection enhanced the neutralization antibody response to the third dose	DM was significantly associated with a decrease in response intensity after completion of the primary vaccine series, but responses to the third dose were generally robust	Small sample size
Santotoribio *et al*[48]	Age, sex, DM, hypertension, heart disease	None	Serum antibody levels were not significantly reduced in patients with common conditions such as arterial hypertension, diabetes, heart disease, or chronic respiratory disease	No assessment of the cell-mediated immune response
Mehta *et al*[49]	DM, immunosuppression, vaccination interval, sex, comorbidity	DM, immunosuppression, and vaccination interval were all significantly associated with anti-RBD antibodies	DM patients had significantly lower titers of anti-spiking antibodies than patients without diabetes	The sample group was patients with autoimmune rheumatic diseases with a high proportion of comorbidities
Ajlan *et al*[50]	DM, type of vaccine, age, triple immunosuppressive therapy, side effects, sex, time since transplantation	Diabetes and triple immunosuppressive therapy appear to significantly affect the immune response. Triple immunosuppressive therapy and age were identified as significant factors in the lack of response to the vaccine after the second dose. Response rates after the first dose of vaccine with the Pfizer vaccine were higher than those with the AstraZeneca vaccine	Diabetes mellitus and triple immunosuppressive therapy appear to significantly affect response	Lack of immunocompetence control group
Billany *et al*[51]	Age, immunosuppression, previous SARS-CoV-2 infection, sex, race, DM	Patients with detectable antibodies were younger than patients without detectable antibodies. Patients who were immunosuppressed were less likely to have detectable antibodies than patients who were not	There was no difference in antibody testing with or without DM	Small sample size

		immunosuppressed. Patients previously infected with COVID-19 were more likely to have detectable antibodies than those with no history of SARS-CoV-2 infection		
Aberer *et al*[52]	TIR, TBR, TAR, T1DM, T2DM, carbohydrate intake, CV	None	At the time of side effects, T1DM patients had significantly less TIR and significantly more TAR, while there was no effect on T2DM patients	Short assessment time and small sample size
Piccini *et al*[53]	Side effects, dose 1, dose 2, TIR, time in different glucose ranges, mean glucose levels, TDD of insulin, bolus proportion, type of vaccine	Side effects after the vaccination were mild and more frequent after the second dose. No severe adverse reactions were reported	No significant differences in glycemic control and glycemic indices were observed at different times throughout the vaccination cycle and were independent of the vaccine type	Small sample size
Heald *et al*[54][1]	Age, BMI, mode of treatment, sex, HbA1c, type of vaccine, duration of diagnosed T1DM	The fall in the percentage BG on target was also greater for those with a median BMI of 28.1 kg/m^2 or more. The fall in the percentage BG on target categorized by additional Metformin/Dapagliflozin was greater than no oral hypoglycemic agents, and the median age ≥ 53 yr was greater than < 53 yr	In T1DM, COVID-19 vaccination can cause a temporary BG disturbance, and this effect is more pronounced in patients taking oral hypoglycemic drugs plus insulin and in the elderly	No analysis of changes in insulin dose in the week following the COVID-19 vaccination
D'Onofrio *et al*[55]	TIR, TBR, TAR, CV, dose 1, dose 2, insulin dosage, SD	None	Pre- and post-CGM data collected during the two vaccine doses did not show any significant differences between the two groups in terms of TIR, TAR, TBR, CV, and SD	Small sample size
Heald *et al*[56][1]	Medication, HbA1c, oral hypoglycemic drugs plus insulin therapy, age, sex, type of vaccine, duration with diabetes, BMI	COVID-19 vaccination can cause a temporary perturbation of interstitial glucose, an effect that is more pronounced in patients taking oral hypoglycemic agents plus insulin. This effect was more pronounced in those with lower HbA1c	In T1DM, vaccination can cause a temporary perturbation of interstitial glucose. There is no difference between the AstraZeneca and the Pfizer vaccines	The effects of the first and second vaccination on interstitial glucose regulation could not be compared
Gouda *et al*[57]	TIR, TDD of insulin, dose 1, dose 2, type of vaccine, insulin dosage, average glucose level, bolus insulin, automated bolus	One week after vaccination, there was a slight decrease in TIR along with an increase in mean blood glucose levels, but both were statistically insignificant	No differences in blood glucose or glycemic perturbations were shown before and after vaccination in patients with T1DM. There was no correlation between vaccine side effects and TIR	The effects of the first and second vaccination on interstitial glucose regulation could not be compared

[1]The authors are the same, but the individual studies are different, including different phases, different samples, and different data.

COVID-19: Coronavirus disease 2019; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; BMI: Body mass index; HbA1c: Glycated hemoglobin; TIR: Time in range; TAR: Time above range; TBR: Time below range; CV: Coefficient variation; TDD: Total daily dose; DM: Diabetes mellitus;T1DM: Type 1 diabetes mellitus; T2DM: Type 2 diabetes mellitus; AESI: Adverse events of special interest; CGM: Continuous glucose monitoring; GMT: Geometric mean titer; GMC: Geometric mean concentration; Abs-RBD-IgG: Anti-SARS-CoV-2 receptor-binding domain IgG; FPG: Fasting plasma glucose; IFG: Impaired fasting glucose; BG: Blood glucose; eGFR: Estimated glomerular filtration rate; COPD: Chronic Obstructive Pulmonary Disease.

here include islet cell injury and acute insulin reduction following entry through the islet angiotensin-converting enzyme 2 (ACE2) receptor[76], cytokine storm[77], oxidative stress, over-activation of the renin-angiotensin-aldosterone system[78], and dysregulation of stress hormone release such as cortisol and catecholamines leading to increased insulin resistance[79]. The vaccine can activate the immune system and inflammatory factors leading to a cytokine storm that reduces pancreatic blood flow or directly impairs β-cell function *via* ACE2 receptors, or the inflammatory response increases the cellular oxidative stress and causes pancreatic fibrosis, resulting in decreased insulin synthesis and secretion and reduced insulin sensitivity in target tissues, thereby elevating blood glucose levels[80]. Pancreatic injury has been reported in individuals following the COVID-19 vaccination, which may be a possible cause of hyperglycemia in individuals following vaccination[81,82]. Of these new-onset diabetic patients listed in Table 2, many exhibited low c-peptide levels, suggesting pancreatic damage. Another possible explanation comes from vaccine excipients, adenoviral vectors, and vaccine SARS-CoV-2 spike protein immunogens that trigger similar mechanisms leading to pancreatic damage and inducing subsequent

hyperglycemic crises. mRNA vaccine was used in 19 of 29 patients and the adenoviral vector vaccine was used in eight. It appears that the mRNA-COVID-19 vaccine was associated with more reports of elevated blood glucose compared to the viral vector vaccine. Although the mRNA-COVID-19 vaccine does not contain an adjuvant, mRNA appears to have self-adjuvant properties that induce autoimmune/inflammatory syndromes and trigger new-onset DM, especially the new-onset T1DM[83].

Vaccination elicits different levels of immune responses within and between individuals and is determined by a range of factors either present within the vaccine, such as the type of adjuvant, or within the host, such as the immune response genes, one or more of which combine to act together. It is important to note that clinicians should remain vigilant for these events, especially for diabetic patients, who require strict glucose monitoring and adequate diabetic treatment in the days following vaccination.

Effect of DM on COVID-19 vaccination

Does vaccination of diabetic patients affect the inherent efficiency of the vaccine? If so, what factors can contribute to these effects?

The efficiency of the vaccine is mainly demonstrated by immunogenicity, neutralizing antibodies, and cellular immunity. Twenty-one of the studies included in this review showed that diabetes decreases the response after vaccination. Marfella *et al*[24] compared the neutralizing antibody titers and antigen-specific CD4 cell responses after the COVID-19 vaccine in a non-diabetic population, a diabetic population with well-regulated glucose (HbA1c ≤ 7%), and a diabetic population with poor regulation (glycosylated hemoglobin > 7%) capacity, the results showed that the rate of neutralizing antibody production and the immune response was significantly reduced in the poorly controlled glycemic population, but that T2DM patients with initially poor glycemic control had improved the immune responses after achieving good glycemic control. Their data underscore the notion that hyperglycemia worsens the immune response and that adequate glycemic control improves the immune response.

The underlying cause of the impaired immune response exhibited by diabetic patients after COVID-19 vaccination is not fully understood and may be related to the dysfunction of the adaptive immune response in diabetic patients. The adaptive immune system can be compromised by poor proliferation in response to antigenic stimuli, impaired production of $CD4^+$ T follicular helper cells, and a reduced ability to produce effector lymphokines. Diabetic patients have reduced numbers of circulating $CD4^+$ cells, reduced $CD4^+$ to $CD8^+$ lymphocyte ratios, reduced lymphocyte proliferative responses, impaired monocytes or macrophages, and defective antigen presentation[84]. Intriguingly, some authors have found that patients with T2DM present with an increased white blood cell counts, but they are more likely to have decreased lymphocytes and more senescent $CD4^+$ and $CD8^+$ T cells[85]. These cells are characterized by overexpression of chemokines (particularly C-X-C motif chemokine receptor type 2) and exhibit altered migratory capacity, resulting in poorer vaccine responses in diabetic patients. In addition, the hyperglycemic environment at the time of vaccination worsens the immunological response and also leads to a decreased immune system response to the vaccine.

Age: Age is one of the most critical factors affecting the production of immunoglobulins and neutralizing antibodies. In general, younger people have a stronger immune response to the COVID-19 vaccine and older people have a reduced immune response to vaccination. B-cell activation is critical for the effectiveness of antibody production, but there are several age-related changes in B-cell function and phenotype. Older adults are usually marked by immune senescence, which may reduce the effectiveness of vaccines[86,87]. The immune response to vaccination is controlled by a delicate balance between effector T cells and follicular T cells, and the aging process disrupts this balance, leading to age-related defects in post-transcriptional regulation, T cell receptor signaling, and metabolic function[88]. The age-related immune responses may be heterogeneous, and co-morbidities and their treatment may also affect the immune response[89]. Therefore, booster vaccines for the elderly may be considered.

Gender: Seven studies observed a stronger immune response after vaccination in women compared to men. Genetic differences as well as sex hormone differences can influence vaccine-induced immunity. X chromosomes express 10 times more genes than Y chromosomes, and differences in gene expression between X and Y chromosomes promote sex differences in vaccine-induced immunity[90]. Testosterone suppresses anti-inflammatory immune cells and promotes a more aggressive T helper cell-type immune response, thereby reducing the immune response to vaccines. In contrast, estrogen has a suppressive effect on pro-inflammatory T cells[91]. In addition, ACE2 receptor expression is influenced by estrogen and correlates with the strength of the immune response[92]. Whether diabetes may interact with gender to influence the extent and persistence of vaccine response is unclear. We found that five of the six studies that observed stronger immune responses in women than in men had study populations from healthcare workers[27,32,35,39,44], and, unquestionably, these studies included a higher proportion of women in their samples, potentially biasing the results.

Type of vaccine and method of vaccination: Surprisingly, Kılınç-Toker *et al*[25] observed that mixed vaccination (CoronaVac plus BioNTech) produced better vaccine efficiency, and similarly, Barocci *et al*[26] found that heterologous vaccination also produced better vaccine efficiency. Wan *et al*[93] observed that two doses of CoronaVac followed by a BNT162b2 heterologous booster may be more effective than

three doses of CoronaVac in a diabetic population. A study comparing the immune responses generated by mRNA-based vaccines and inactivated whole virus particle vaccines found that mRNA-based vaccines induced stronger humoral immune responses and higher levels of cellular responses than inactivated whole virus particle vaccines[94]. Adenoviral vectors carry antigens that can persist for long periods of time. Anti-glycoprotein IgG antibodies persist until day 180 after single-dose vaccination with ChAd3-EBO-Z in phase 1/2a clinics[95], and antibody responses to a single dose of ChAdOx1 (AZD1222) vaccine have a long half-life[96]. The mixed vaccination may combine the respective advantages of the different vaccine types, while the robust humoral response induced by the heterologous booster may be attributed to the extended interval between the primary and booster doses. Extended intervals between booster doses may result in higher neutralizing activity and a more extensive humoral response through germinal center responses, including somatic cell hypermutation and affinity maturation[97]. Evidence from several studies suggests that heterologous inoculation is safe and effective and induces a robust humoral response to SARS-CoV-2, allowing for faster protection of the target population[98-100].

Obesity: Adipose tissue is another metabolic organ with high ACE2 Levels that may exhibit a propensity for SARS-CoV-2 and is also a source of inflammatory adipokines and cytokines that regulate glucose and insulin resistance. A previous study suggested that excess adipose tissue may impede nutrient supply to immune cells[101]. Obesity leads to adipocyte hypertrophy, which induces low levels of inflammation and insulin resistance[102]. In addition, the hyperleptinemia and hyperinsulinemia that accompany the obese state contribute to T-cell dysfunction, leading to impaired immune responses [103]. These mechanisms of immune cell suppression can reduce antibody production after vaccination.

Special Populations: Patients with autoimmune rheumatic diseases, hemodialysis patients, and organ transplant patients, a special group with high comorbidity and impaired immune response, have significantly lower antibody titers established after vaccination, and the persistence of IgG titers may follow different kinetics. Billany *et al*[51] described 94 patients on maintenance hemodialysis (including 43 diabetic patients) at the first dose of vaccine antibody response 28 d after vaccination. The results showed that neutralizing antibodies were detectable in 75 patients (79.8%), and there was no difference in the presence or absence of diabetes on antibody detection in the cohort. Reassuringly, Agur *et al*[104] expressed the same notion. Ajlan *et al*[50] evaluated the efficacy and safety of two different vaccine platforms in 431 patients with liver or kidney solid organ transplants (191 of whom were diabetic patients), and they found no difference in efficacy between the two vaccine platforms in solid organ transplant patients, with response unresponsiveness primarily related to DM. Bieber *et al*[105] also reached similar conclusions. These findings seem to support the notion that both vaccination and booster use in immunodeficient populations are associated with better COVID-19-related outcomes, and therefore, regardless of the presence of diabetes, they should be encouraged to receive booster vaccinations to obtain vaccine protection that may be close to that obtained in the general population after two doses, and that combination or allogenic vaccination is a vaccination strategy worth considering for them.

Adverse reactions: Of the 54 studies included, the earliest study began in November 2020, only two years ago so far. SARS-CoV-2 is a novel virus in the history of human viruses, and the COVID-19 vaccine is even more novel for the human being as a whole, given the incredible speed with which many vaccines were developed during the period of COVID-19. It is too early to observe from just two years how the vaccine affects the life cycle of patients with pre-existing DM, so the effect of the COVID-19 vaccine on the natural course of diabetes is more in the form of observed adverse effects. Ten studies mentioned adverse reactions after vaccination, and only Lee *et al*[32] claimed that diabetes had an increased risk of grade 3 to 4 adverse reactions, while most studies expressed that people with DM were less likely to experience significant side effects after COVID-19 vaccination compared to healthy individuals. The most common systemic side effects are headache, chills, fever, and fatigue, and local effects are pain, redness, and swelling at the injection site. Most side effects are mild and disappear within a few days after vaccination and do not interfere with daily activities. Even for those patients diagnosed with new-onset DM or hyperglycemic crisis, their symptoms resolved rapidly with reasonable treatment, and there was not a single case of death. Although some very rare and serious vaccine-related adverse events have also been reported in myocarditis[106], myocardial infarction[107], and Green-Barre syndrome[21], the vast majority of studies have concluded that vaccination is safe in patients with DM.

Understanding the factors associated with the strength of the immune response to these vaccines and the adverse effects associated with vaccine safety is necessary to optimize vaccination programs. These findings support prioritizing vaccination of vulnerable populations such as diabetes and completing the vaccination cycle, and in countries where conditions permit, promoting the use of booster doses, especially for those special groups with impaired immune responses.

Explanation of "no effect" between DM and vaccination

Of the 54 studies included, a total of 12 studies indicated a "no effect" relationship between DM and

vaccination. Piccini *et al*[53] used two types of vaccines in 39 patients over 16 years of age with T1DM who were vaccinated for the entire cycle and showed that no significant differences were observed in time in range, time in different glucose ranges, mean glucose levels, total daily dose of insulin, or bolus ratios before and after any dose or before and after the entire vaccination cycle. They used a hybrid closed-loop system to exclude the effect on glucose brought about by automatic insulin correction of the treatment system. No serious adverse reactions were reported, although minor post-vaccination side effects were observed. Similarly, another study expressed the same opinion[55]. In a prospective multicenter cohort study analyzing T1DM and T2DM patients as well as healthy controls, it was found that anti-SARS-CoV-2 S receptor binding domain antibody levels after the second vaccination were comparable in healthy controls and in patients with T1DM and T2DM, independent of glycemic control. Papadokostaki *et al*[46] also confirmed this notion. These studies suggest that vaccination has no effect on glycemia in patients with DM, regardless of the vaccine type and before and after vaccination; also, DM has no effect on vaccine efficacy or safety. We analyzed the possible reasons for the differences in the results of these 12 studies compared to other studies: First, when the effect of blood glucose on vaccination was studied, it was done in healthy or special populations and not specifically designed for diabetic populations, for example, Billany *et al*'s study[51] was from a hemodialysis population. In addition, the number of diabetic patients included in these studies was very low. The number of diabetic patients in these two studies was 39 and 35, respectively. Therefore, the results cannot be extrapolated to all diabetic patients. Second, the clinical characteristics of the diabetic subgroups in these studies were not sufficient to explain the heterogeneity of the immune response. The confounding factors of diabetics such as age, type of diabetes, severity of the disease, course of the disease, and therapeutic schedule may affect the results to some extent. Third, heterogeneity in assay methods, differences in the timing of antibody detection (whether it coincides with the lowest value of antibody titers), and differences in the period studied (whether it is affected by a mutant strain that exhibits antibody unresponsiveness) can lead to differences in the immune response to vaccination among vaccinated individuals. Although these differences were faced in other studies as well, it is possible that in these 12 studies, it happened to intersect with more factors and showed inconsistent results with other studies.

Combining the findings of these studies, we can infer that although vaccination gives diabetic patients more possible risk of causing elevated blood glucose than the general population, after vaccination, there is a lower antibody response in diabetic patients compared with healthy subjects, but there is still a considerable amount and intensity of the vaccine immune response, and overall the second dose immune response is higher than the first dose, and diabetic patients with good glycemic control and vaccination with the second dose, the immune response can be significantly improved, and booster vaccination is advocated in special populations subject to immunosuppression, the immune response from mixed vaccination is better than that from a single vaccine type, and heterologous vaccination is better than homologous vaccination.

Advantages and limitations and future directions

This is the first systematic review to date to comprehensively analyze the bidirectional effects of COVID-19 vaccination and DM. First, the question about the interaction of DM and vaccination is a novel one, and our review addresses a very clinically relevant question that both physicians and patients are eager to answer. Second, the studies included in this review include a variety of special populations, including pediatric diabetes, hemodialysis, solid organ transplantation, and autoimmune disease populations, as well as a broad representation of patients with two major types of diabetes, which can inform vaccination strategies for patients with DM on a larger scale. Finally, our study data are from real-world sources, providing real and reliable information for optimizing vaccination in this vulnerable population with DM and providing objective and qualitative evidence for future public policy formulation and optimal vaccine strategies.

Of course, there are some limitations to this systematic review. First, as described in Strengths, the wide representation of the included populations also implies large heterogeneity. Population heterogeneity includes, in addition to the common heterogeneity in demographic characteristics, the health-seeking behavior of these populations and the geographic distribution of the population, and these heterogeneities can introduce bias into the interpretation of the overall results. Second, the small sample size of some studies, with a total of 18 cases (series) reported, and the small proportion of people with DM in some studies limit the ability to test for possible differential effects between subgroups. Third, possibly because of ethical challenges in clinical practice, no randomized controlled studies were found among the included studies, although some authors made their best efforts to reduce potential bias from selection by using PSM methods. Finally, important reports not published in English may have been omitted from this review, or the search strategy failed to capture them.

In the world of the COVID-19 vaccine and DM, many questions remain: How frequent is the new-onset of DM after COVID-19 vaccination? Which component of the vaccine is more likely to cause dysglycemia and will COVID-19 vaccine heterologous vaccination reduce adverse events in patients with diabetes? Our systematic review implies some gaps in the literature that could be addressed in the future. Studies on the effects of COVID-19 vaccination on DM in type 1 and type 2 for comparative analysis and studies on changes in the effects of vaccination on the cellular immunity in patients with

DM and the effects of vaccination on the natural course of pre-existing DM are scarce, and there is a need for longer follow-up or well-designed large-scale studies in the future to further provide an updated and more comprehensive evidence-based basis for the relationship between DM and COVID-19.

CONCLUSION

In conclusion, there is a complex relationship between vaccination and DM with bidirectional effects. Vaccination may contribute to the risk of worsening glycemia in diabetic patients, and diabetic patients may have a lower antibody response after vaccination than the general population, but good glycemic control can significantly improve the immune response.

ARTICLE HIGHLIGHTS

Research background

Both coronavirus disease 2019 (COVID-19) and diabetes pose a serious threat to human health. Vaccination is an effective way to prevent the spread of COVID-19. There are few and conflicting data on the interaction between COVID-19 vaccination and diabetes mellitus.

Research motivation

We searched all current clinical studies to explore the complex relationship between COVID-19 vaccination and diabetes.

Research objectives

We analyzed various factors and possible mechanisms of the interaction between COVID-19 vaccination and diabetes in order to inform the optimal vaccination strategy and clinical management of patients with diabetes.

Research methods

We comprehensively searched PubMed, MEDLINE, and EMBASE online databases and the grey literature of medRxiv and bioRxiv using keywords individually or in combination, with a cut-off date of December 2, 2022. We followed the inclusion and exclusion criteria and studies with quantifiable evidence were included in the full-text review. We also manually searched for important references cited by the included studies.

Research results

A total of 54 studies were included. The earliest study began in November 2020. Thirty studies discussed the effect of diabetes on COVID-19 vaccination, with the majority indicating that diabetes decreases the response to vaccination. Of the other 24 studies on the effect of vaccination on diabetes, most concluded that vaccination was associated with a risk of elevated blood glucose. Twelve of the 54 studies expressed a "no effect" relationship between diabetes and vaccination.

Research conclusions

There is a bidirectional relationship between vaccination and diabetes. Vaccination may contribute to the risk of elevated blood glucose in diabetic patients, and diabetes may have a lower antibody response after vaccination than in the general population, but good glycemic control can significantly improve the immune response.

Research perspectives

Our review reveals a complex relationship between diabetes and vaccination and suggests some gaps in the literature that can be addressed in the future, necessitating well-designed large-scale studies to further provide a more comprehensive basis for the relationship between diabetes and COVID-19.

ACKNOWLEDGEMENTS

Many thanks to Mr. Han Boning for editing the manuscript, polishing the English, and providing the audio for the core tip of the manuscript. Many thanks to Mr. Zhao Kai for his help in English correction during the manuscript revision process.

FOOTNOTES

Author contributions: He YF designed the study, reviewed literature, and drafted the manuscript; Ouyang J, Hu XD and Wu N retrieved and summarized the literature; Jiang ZG, Bian N and Wang J advised on the review and reviewed the final manuscript; All authors have read and approved the final manuscript.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

Country/Territory of origin: China

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S-Editor: Li L
L-Editor: A
P-Editor: Fan JR

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