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

Correlation between COVID-19 vaccination and diabetes

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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, and EMBASE online databases, 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 publications, 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 350,963. 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

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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.

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.

Figure 1 Flow diagram of literature search.

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 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 diabetes mellitus (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 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 diabetes mellitus (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 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* also implied that COVID-19 vaccination can cause temporary relative hyperglycemia in patients with T1DM[54]. 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 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*[23] 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 days 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 (TIR), time in different glucose ranges, mean glucose levels, total daily dose (TDD) 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 was from a hemodialysis population[51]. 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 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 DM.

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.

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