Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Diabetes & Metabolic Syndrome: Clinical Research & Reviews 15 (2021) 505–508

Contents lists available at ScienceDirect

Diabetes & Metabolic Syndrome: Clinical Research & Reviews

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

COVID-19 vaccination in patients with diabetes mellitus: Current concepts, uncertainties and challenges

Rimesh Pal [a], Sanjay Kumar Bhadada [a, *], Anoop Misra [b, c, d, **]

[a] Department of Endocrinology, Post Graduate Institute of Medical Education and Research, Chandigarh, 160012, India
[b] Centre of Nutrition & Metabolic Research (C-NET), National Diabetes, Obesity and Cholesterol Foundation (N-DOC), SDA, New Delhi, India
[c] Diabetes Foundation (India), SDA, New Delhi, India
[d] Fortis C-DOC Centre of Excellence for Diabetes, Metabolic Diseases and Endocrinology, Chirag Enclave, Nehru Place, New Delhi, India

ARTICLE INFO

Article history:
Received 15 February 2021
Received in revised form
17 February 2021
Accepted 19 February 2021

Keywords:
COVID-19
Vaccines
Diabetes mellitus

ABSTRACT

Background and aims: To summarize the available evidence on the use COVID-19 vaccines in patients with diabetes mellitus.
Methods: We performed a thorough literature search with regard to COVID-19 vaccines in patients with type 1 and type 2 diabetes mellitus.
Results: The novel coronavirus disease (COVID-19) tends to portend a poor prognosis in patients with diabetes mellitus (DM). Primary prevention remains the mainstay for mitigating the risks associated with COVID-19 in patients with DM. A significant step in primary prevention is timely vaccination. Routine vaccination against pneumococcal pneumonia, influenza, and hepatitis B is recommended in patients with DM with good efficacy and reasonable safety profile. With clinical data supporting a robust neutralizing antibody response in COVID-19 patients with DM, vaccination in individuals with DM is justified. In fact, as the burden of the disease is borne by people with DM, *COVID-19 vaccination should be prioritized in individuals with DM.* Multiple unresolved issues with regard to preferred vaccine type, vaccine efficacy and durability, frequency of administration, vaccination in children (<18 years) and pregnant/lactating women however remain, and need to be addressed through future research.
Conclusions: Patients with type 1 and type 2 diabetes mellitus are at a high risk of poor prognosis with COVID-19 and vaccination should be prioritized in them. However, many unresolved issues with regard to COVID-19 vaccination need to be addressed through future research.

The novel coronavirus disease (COVID-19) has affected over 100 million people and inflicted over 2 million deaths globally. The disease portends a poor prognosis especially in patients with diabetes mellitus (DM). Diabetes mellitus is associated with severe disease, intensive care unit admissions, and increased mortality in patients with COVID-19 [1–5].

Several recent studies have shown that both patients with type 2 diabetes (T2D) and type 1 diabetes (T1D) have an increased vulnerability to severe illness from COVID-19 compared with people without DM. In relative terms, patients with T1D and those with T2D had similar adjusted odds ratios (ORs) for hospitalization (3.90 for T1D *vs.* 3.36 for T2D), severity of illness (3.35 *vs.* 3.42) [6], and in-hospital mortality (3.51 *vs.* 2.02) [7]. Besides, good glycemic control before hospital admission, as indicated by glycated hemoglobin (HbA_{1c}), has not been consistently associated with improved outcomes in patients with DM admitted for COVID-19 [8]. Thus, primary prevention remains the mainstay for mitigating the risks associated with COVID-19 in patients with DM.

A significant step in primary prevention of infections is timely and appropriate vaccination. Routine vaccination against pneumococcal pneumonia, influenza, and hepatitis B is recommended in patients with DM [9]. Although prior studies have shown impaired antibody response to influenza and hepatitis B vaccines in patients with DM [10,11], with recent advances in the development of vaccines, people with DM are able to mount an appropriate immune response post-vaccination. In multiple case-control studies, the efficacy and safety of pneumococcal vaccine have been reported as

* Corresponding author.
** Corresponding author. Centre of Nutrition & Metabolic Research (C-NET), National Diabetes, Obesity and Cholesterol Foundation (N-DOC), SDA, New Delhi, India.
E-mail addresses: bhadadask@rediffmail.com (S.K. Bhadada), anoopmisra@gmail.com (A. Misra).

https://doi.org/10.1016/j.dsx.2021.02.026
1871-4021/

Table 1
Summarizing the data on the available COVID-19 vaccines.

Name of vaccine	Company/organization of origin	Type	Trial phase	Efficacy[a]	Safety	Representation of participants with DM
BNT162b2 [21]	Pfizer-BioNTech USA, Germany	Lipid nanoparticle −formulated, nucleoside-mRNA vaccine that encodes a prefusion stabilized, membrane-anchored SARS-CoV-2 spike glycoprotein.	2/3	95%	Short-term, mild-to-moderate pain at the injection site, fatigue, and headache. Incidence of serious adverse events low and similar in vaccine and placebo groups.	Not mentioned
mRNA-1273 [22]	Moderna and the Vaccine Research Center at NIAID USA	Lipid-nanoparticle-encapsulated mRNA vaccine expressing the prefusion-stabilized SARS-CoV-2 spike glycoprotein	3	94.1%	Transient local and systemic reactions, incidence of serious adverse events low and similar in vaccine and placebo groups.	Yes (n = 2875)
AZD1222 (ChAdOx1) [23]	Oxford-AstraZeneca Jenner Institute, University of Oxford England	Recombinant, replication-deficient chimpanzee adenoviral vector ChAdOx1, containing the SARS-CoV-2 spike glycoprotein antigen.	1/2/3	70.4%	Good safety profile with serious adverse events and adverse events of special interest balanced across the study arms.	Yes (n = 270)
Sputnik V vaccine (Gam-COVID-Vac) [24]	Gamaleya Research Institute of Epidemiology and Microbiology Russia	Combined vector vaccine, based on recombinant adenovirus (rAd) type 26 and rAd type 5—both of which carry the gene for SARS-CoV-2 spike glycoprotein.	3	91.6%	Common adverse events were flu-like illness, injection site reactions, headache, and asthenia. None of the serious adverse events were considered associated with vaccination.	Yes (n = 4922) [b]
NVX-CoV2373 [25]	Novavax, Inc. USA	Matrix-M1 adjuvant and recombinant SARS-CoV-2 nanoparticle vaccine, constructed from the full-length, wild-type SARS-CoV-2 spike glycoprotein	3	89.3%	Severe, serious, and medically attended adverse events occurred at low levels and balanced between vaccine and placebo groups.	NA
CoronaVac [26]	Sinovac Biotech China	Inactivated vaccine candidate against COVID-19	3	50.65%−91.25%	NA	NA
JNJ-78436735 or Ad26.COV2.S [27]	Johnson & Johnson (Janssen Biotech, Inc.) USA	Recombinant, replication-incompetent adenovirus serotype 26 (Ad26) vector encoding a full-length and stabilized SARS-CoV-2 spike protein.	3	66%	No report of significant safety concerns. Overall fever rates were 9% and Grade 3 fever 0.2%. Overall serious adverse events reported were higher in participants who received placebo as compared to the active vaccine candidate.	Yes (n = 2764)
COVAXIN (BBV152) [c] [28]	Bharat Biotech India	Whole-virion inactivated SARS-CoV-2 vaccine formulated with a toll-like receptor 7/8 agonist molecule adsorbed to alum (Algel-IMDG) or alum (Algel).	1 [d]	NA	Common solicited adverse events were injection site pain, headache, fatigue, fever, and nausea or vomiting. All adverse events were mild or moderate. No significant differences were observed between the vaccinated and control groups.	NA
COVISHIELD (ChAdOx1) [c] [29]	Serum Institute India	Recombinant, replication-deficient chimpanzee adenoviral vector ChAdOx1, containing the SARS-CoV-2 spike glycoprotein antigen with *technology transfer from Oxford/AstraZeneca.*	NA [e]	NA [e]	NA [e]	NA [e]

NA: Not available, SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2, IMDG: Imidazoquinoline, USA: The United States of America, NIAID: National Institute of Allergy and Infectious Diseases.

[a] The efficacy pertains to the usual strain of SARS-CoV-2.
[b] Included participants with diabetes, ischemic heart disease, hypertension, obesity.
[c] Drug Controller General of India (DCGI) approval for restricted use in emergency situation received.
[d] Phase III clinical trial of COVAXIN™ is ongoing in India.
[e] Phase II/III clinical trials of COVISHIELD™ are ongoing in India. However, robust data on phase 1/2/3 trials of the Oxford-AstraZeneca vaccine are available.

Table 2
Summarizing the possible issues regarding the use of COVID-19 vaccines in patients with diabetes mellitus. COVID-19: Novel coronavirus disease, SARS-CoV-2: Severe acute respiratory syndrome 2.

Which vaccine is to be preferred?
How effective would the COVID-19 vaccines be in the real world?
How durable would the protection be in the real world?
Would COVID-19 vaccination need to be repeated semi-annually or annually?
Would COVID-19 vaccination be justified in a child or adolescent (<16 years) with diabetes mellitus?
Are COVID-19 vaccines safe in pregnant or lactating women with diabetes mellitus?
Would complications in patients with longstanding diabetes mellitus (like chronic kidney disease) affect vaccine efficacy and/or durability?
Could COVID-19 vaccines be administered in the presence of active infections which are otherwise common in patients with diabetes mellitus?
Could anti-diabetic drugs modulate the efficacy of COVID-19 vaccines?
Would serious adverse events following COVID-19 vaccination be more frequent?
Would vaccination with the currently available COVID-19 vaccines be less effective in view of the rapid development of new strains of the SARS-CoV-2?
Could mixing of COVID-19 vaccines boost immune response?

ranging from 56% to 81% [12,13]. Likewise, the efficacy of 23-valent pneumococcal polysaccharide vaccine (PPV23) was found to be 84% in people with DM [14]. The 23-valent pneumococcal polysaccharide vaccination effectively prevented pneumococcal diseases and reduced utilization of medical services in elderly patients with DM aged 75 and more [15]. Furthermore, young and older adults with DM have been shown to mount optimal B-cell response to seasonal influenza vaccine [16]. Adults with T2D considerably benefit from influenza vaccination in terms of reduction in any complications, hospitalizations, and death [17]. Hence, these vaccinations have been included in the standard care for patients with DM.

Adverse effects following vaccination in patients with DM are usually mild. In a diabetes clinic in India, 1568 patients (duration > 5.3 years) with DM were vaccinated against pneumonia and influenza. The only side effects observed were aches or pain in joints or muscles, fever, local rash, or swollen glands. No severe allergic reactions were reported. Out of 2057 patients with DM who underwent pneumococcal vaccinations, only 17 reported mild pain and redness at the injection site [12].

Multiple vaccines with varying efficacy and safety have been developed against COVID-19 [18–26]. In India, COVAXIN™ and COVISHIELD™ have been approved by the Drug Controller General of India (DCGI) for restricted use in emergency situation. However, considering the paucity of data in participants with DM in the hitherto available clinical trials (Table 1), the use of COVID-19 vaccines in this subgroup of subjects needs more research.

Hitherto, data with regard to immune response in DM patients with COVID-19 are limited. One preliminary report from India had demonstrated impaired anti-SARS-CoV-2 response in non-severe COVID-19 patients with T2D. Total anti-SARS-CoV-2 antibody (IgG + IgM), as measured by electrochemiluminescence immunoassay, were undetectable in 3 out of 9 patients with T2D when estimated at a median (interquartile range) of 16 days post-polymerase chain reaction (PCR) confirmation of COVID-19 diagnosis [27]. However, a study from Italy that had included 150 COVID-19 patients, 40 of whom had DM, showed that the presence of DM and hyperglycemia did not affect the kinetics and durability of the neutralizing antibody response against the SARS-CoV-2 spike protein. Neutralizing antibody positivity after hospital admission was evident in 70% and 75% of subjects without and with DM, respectively. Neutralizing antibody positivity and neutralization titres increased throughout the observation period, from week 1 to week 3. After the first follow-up visit at 1-month, neutralizing antibodies declined but robust neutralizing activity was still present at the last planned follow-up visit at 6 months in patients with and without DM. Besides, positivity for neutralizing antibodies at the time of hospital admission conferred protection against mortality in patients with and without DM [28]. Similarly, another study from Italy showed that the humoral immune response against SARS-CoV-2 in patients with DM was present and almost superimposable, as for timing and antibody titres, to that of non-diabetic patients and was not influenced by glucose levels. Positivity for IgG against the SARS-CoV-2 spike receptor-binding domain (RBD) was predictive of survival rate, both in the presence or absence of DM [29]. These data provide the rationale to include patients with DM in the vaccination campaign against SARS-CoV-2.

The World Health Organization (WHO) Strategic Advisory Group of Experts (SAGE) on Immunization has recommended the use of the Oxford-AstraZeneca vaccine (AZD1222) in people with comorbidities that have been identified as increasing the risk of severe COVID-19. The comorbidities studied in the clinical trials included obesity, cardiovascular disease, respiratory disease and *diabetes* [30]. The Centers for Disease Control and Prevention (CDC), in lieu with the suggestions provided by the Advisory Committee on Immunization Practices (ACIP) has recommended that the initial supplies of COVID-19 vaccine be allocated to healthcare personnel and long-term care facility residents. This is referred to as Phase 1a. Subsequently, vaccination is to be provided as a part of Phase 1b and Phase 1c. Phase 1c includes people aged 16–64 years with underlying medical conditions which increase the risk of serious, life-threatening complications from COVID-19. Among others, T2D is included as one of the medical conditions [31]. The Diabetes UK

Table 3
Summarizing the possible areas of future research focus with regard to COVID-19 vaccination in patients with diabetes mellitus. COVID-19: Novel coronavirus disease, SARS-CoV-2: Severe acute respiratory syndrome 2.

Inclusion of sufficient number of patients with diabetes mellitus in phase 3 clinical trials evaluating COVID-19 vaccine efficacy
Comparison of COVID-19 vaccine efficacy in patients with type 1 and type 2 diabetes mellitus
Head-to-head comparison of efficacy of various COVID-19 vaccines in patients with diabetes mellitus
Comparison of COVID-19 vaccine efficacy in patients with diabetes mellitus with variable glycemic control
Evaluation of COVID-19 vaccine efficacy in children and adolescents (<16 years) with diabetes mellitus
Evaluation of COVID-19 vaccine efficacy in elderly with diabetes mellitus
Evaluation of COVID-19 vaccine efficacy in patients with diabetes mellitus and multiple micro- and/or macrovascular complications
Effect of COVID-19 vaccination on glycemic control in patients with diabetes mellitus
Robust post-marketing surveillance of COVID-19 vaccine safety in patients with diabetes mellitus

has also prioritized COVID-19 vaccination in patients with DM [32]. However, none of the vaccines have been tested in children or adolescents <16–18 years of age (Pfizer-BioNTech COVID-19 vaccine is authorized for use in persons aged 16–17 years), hence, routine vaccination of subjects with DM in this age group is not yet recommended. This would necessarily imply that while most people with T2D would be ideal candidates for COVID-19 vaccines, many patients with T1D would be deprived of the same. In addition, multiple other questions with regard to COVID-19 vaccination exist that have been summarized in Table 2.

The choice of the vaccine remains a major issue and in lieu of the limited clinical evidence, it should be guided by availability; in the Indian setting, with no data available from phase 3 clinical trials, either COVAXIN™ or COVISHIELD™ could be used for vaccinating patients with DM. Further research focusing on many unresolved issues is warranted (Table 3).

Funding

None.

Declaration of competing interest

None to declare.

Acknowledgements

None.

References

[1] Pal R, Bhadada SK. COVID-19 and diabetes mellitus: an unholy interaction of two pandemics. Diabetes Metab Syndr 2020;14:513–7.
[2] Mithal A, Jevalikar G, Sharma R, Singh A, Farooqui KJ, Mahendru S, et al. High prevalence of diabetes and other comorbidities in hospitalized patients with COVID-19 in Delhi, India, and their association with outcomes. Diabetes Metab Syndr 2021;15:169–75.
[3] Pal R, Bhadada SK. Managing common endocrine disorders amid COVID-19 pandemic. Diabetes Metab Syndr 2020;14:767–71.
[4] Pal R, Bhansali A. COVID-19, diabetes mellitus and ACE2: the conundrum. Diabetes Res Clin Pract 2020;162:108132.
[5] Huang I, Lim MA, Pranata R. Diabetes mellitus is associated with increased mortality and severity of disease in COVID-19 pneumonia – a systematic review, meta-analysis, and meta-regression. Diabetes Metab Syndr 2020;14:395–403.
[6] Gregory JM, Slaughter JC, Duffus SH, Smith TJ, LeStourgeon LM, Jaser SS, et al. COVID-19 severity is tripled in the diabetes community: a prospective analysis of the pandemic's impact in type 1 and type 2 diabetes. Diabetes Care 2021;44:526–32.
[7] Barron E, Bakhai C, Kar P, Weaver A, Bradley D, Ismail H, et al. Associations of type 1 and type 2 diabetes with COVID-19-related mortality in England: a whole-population study. Lancet Diabetes Endocrinol 2020;8:813–22.
[8] Cariou B, Hadjadj S, Wargny M, Pichelin M, Al-Salameh A, Allix I, et al. Phenotypic characteristics and prognosis of inpatients with COVID-19 and diabetes: the CORONADO study. Diabetologia 2020;63:1500–15.
[9] American Diabetes Association. 4. Comprehensive medical evaluation and assessment of comorbidities: *Standards of medical Care in diabetes—2020*. Diabetes Care 2020;43:S37–47.
[10] Smith SA, Poland GA. Use of influenza and pneumococcal vaccines in people with diabetes. Diabetes Care 2000 Jan;23:95–108.
[11] Volti SL, Caruso-Nicoletti M, Biazzo F, Sciacca A, Mandara G, Mancuso M, et al. Hyporesponsiveness to intradermal administration of hepatitis B vaccine in insulin dependent diabetes mellitus. Arch Dis Child 1998;78:54–7.
[12] Kesavadev J, Misra A, Das A, Saboo B, Basu D, Thomas N, et al. Suggested use of vaccines in diabetes. Indian J Endocrinol Metab 2012;16:886.
[13] Shapiro ED. Prevention of pneumococcal infection with vaccines: an evolving story. J Am Med Assoc 2012;307:847–9.
[14] Butler JC, Breiman RF, Campbell JF, Lipman HB, Broome CV, Facklam RR. Pneumococcal polysaccharide vaccine efficacy. An evaluation of current recommendations. J Am Med Assoc 1993;270:1826–31.
[15] Kuo C-S, Lu C-W, Chang Y-K, Yang K-C, Hung S-H, Yang M-C, et al. Effectiveness of 23-valent pneumococcal polysaccharide vaccine on diabetic elderly. Medicine (Baltim) 2016;95:e4064.
[16] Frasca D, Diaz A, Romero M, Mendez NV, Landin AM, Ryan JG, et al. Young and elderly patients with type 2 diabetes have optimal B cell responses to the seasonal influenza vaccine. Vaccine 2013;31:3603–10.
[17] Looijmans-Van den Akker I, Verheij TJM, Buskens E, Nichol KL, Rutten GEHM, Hak E. Clinical effectiveness of first and repeat influenza vaccination in adult and elderly diabetic patients. Diabetes Care 2006;29:1771–6.
[18] Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and efficacy of the BNT162b2 mRNA covid-19 vaccine. N Engl J Med 2020;383:2603–15.
[19] Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N Engl J Med 2021;384:403–16.
[20] Voysey M, Clemens SAC, Madhi SA, Weckx LY, Folegatti PM, Aley PK, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. Lancet 2021;397:99–111.
[21] Logunov DY, Dolzhikova IV, Shcheblyakov DV, Tukhvatulin AI, Zubkova OV, Dzharullaeva AS, et al. Safety and efficacy of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine: an interim analysis of a randomised controlled phase 3 trial in Russia. Lancet 2021. S0140673621002348.
[22] Novavax COVID-19 vaccine demonstrates 89.3% efficacy in UK phase 3 trial [Internet]. [cited 2021 Aug 2]. Available from: https://ir.novavax.com/news-releases/news-release-details/novavax-covid-19-vaccine-demonstrates-893-efficacy-uk-phase-3.
[23] Sinovac announces phase III results of its COVID-19 vaccine. https://www.businesswire.com/news/home/20210205005496/en/Sinovac-Announces-Phase-III-Results-of-Its-COVID-19-Vaccine.
[24] Johnson & johnson announces single-shot janssen COVID-19 vaccine candidate met primary endpoints in interim analysis of its phase 3 ENSEMBLE trial. https://www.jnj.com/johnson-johnson-announces-single-shot-janssen-covid-19-vaccine-candidate-met-primary-endpoints-in-interim-analysis-of-its-phase-3-ensemble-trial.
[25] Ella R, Vadrevu KM, Jogdand H, Prasad S, Reddy S, Sarangi V, et al. Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBV152: a double-blind, randomised, phase 1 trial. Lancet Infect Dis 2021. S1473309920309427.
[26] ChAdOx1 nCoV- 19 corona virus vaccine (recombinant) COVISHIELDTM [Internet]. [cited 2021 Aug 2]. Available from: https://www.seruminstitute.com/product_covishield.php.
[27] Pal R, Sachdeva N, Mukherjee S, Suri V, Zohmangaihi D, Ram S, et al. Impaired anti-SARS-CoV-2 antibody response in non-severe COVID-19 patients with diabetes mellitus: a preliminary report. Diabetes Metab Syndr 2021;15:193–6.
[28] Dispinseri S, Lampasona V, Secchi M, Cara A, Bazzigaluppi E, Negri D, et al. Robust neutralizing antibodies to SARS-CoV-2 develop and persist in subjects with diabetes and COVID-19 pneumonia. J Clin Endocrinol Metab 2021;dgab055.
[29] Lampasona V, Secchi M, Scavini M, Bazzigaluppi E, Brigatti C, Marzinotto I, et al. Antibody response to multiple antigens of SARS-CoV-2 in patients with diabetes: an observational cohort study. Diabetologia 2020;63:2548–58.
[30] Interim recommendations for use of the AZD1222 (ChAdOx1-S [recombinant]) vaccine against COVID- 19 developed by Oxford University and AstraZeneca [Internet]. [cited 2021 Nov 2]. Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE_recommendation-AZD1222-2021.1.
[31] The advisory committee on immunization Practices' updated interim recommendation for allocation of COVID-19 vaccine — United States, december 2020 [Internet]. [cited 2021 Nov 2]. Available from: https://www.cdc.gov/mmwr/volumes/69/wr/mm695152e2.htm?s_cid=mm695152e2_w.
[32] Coronavirus vaccines and diabetes [Internet]. [cited 2021 Aug 2]. Available from: https://www.diabetes.org.uk/about_us/news/coronavirus-vaccines.