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

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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.

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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 (HbA1c), 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...
### Table 1
Summarizing the data on the available COVID-19 vaccines.

| Name of vaccine                  | Company/organization of origin | Type                                                                 | Trial phase | Efficacy | 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 asthma. None of the serious adverse events were considered associated with vaccination. Severe, serious, and medically attended adverse events occurred at low levels and balanced between vaccine and placebo groups. | 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              | Bharat Biotech India            | Whole-vision 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           | 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.
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 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.

| Question                                                                 | Answer                                                                 |
|--------------------------------------------------------------------------|------------------------------------------------------------------------|
| 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?                 |                                                                      |

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.

| Research Focus                                                                 | Details                                                                 |
|-----------------------------------------------------------------------------|------------------------------------------------------------------------|
| 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]. 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).

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None to declare.

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