**Name of Journal:** *World Journal of Diabetes*

**Manuscript NO:** 82328

**Manuscript Type:** MINIREVIEWS

**COVID-19 vaccination and diabetic ketoacidosis**

Joob B *et al*. COVID-19 vaccination and DKA

Beuy Joob, Viroj Wiwanitkit

**Beuy Joob,** Academic Center, Sanitation1 Medical Academic Center, Bangkok 1033300, Thailand

**Viroj Wiwanitkit,** Community Medicine, DY Patil Vidhyapeeth, Pune 233230, India

**Author contributions:** Joob B and Wiwanitkit V contributed equally to this work; Joob B and Wiwanitkit V give the ideas; Joob B wrote and analyzed the data; Wiwanitkit V supervised; All authors have read and approve the final manuscript.

**Corresponding author: Beuy Joob, PhD, Adjunct Associate Professor,** Academic Center, Sanitation1 Medical Academic Center, Bangkok 1033300, Thailand. beuyjoob@hotmail.com

**Received:** December 15, 2022

**Revised:** February 1, 2023

**Accepted:** April 12, 2023

**Published online:**

**Abstract**

An efficient coronavirus disease 2019 (COVID-19) vaccine is urgently required to fight the pandemic due to its high transmission rate and quick dissemination. There have been numerous reports on the side effects of the COVID-19 immunization, with a focus on its negative effects. Clinical endocrinology is extremely interested in the endocrine issue that arises after receiving the COVID-19 vaccine. As was already mentioned, after receiving the COVID-19 vaccine, many clinical problems could occur. Additionally, there are some compelling reports on diabetes. After receiving the COVID-19 vaccine, a patient experienced hyperosmolar hyperglycemia state, a case of newly-onset type 2 diabetes. There has also been information on a potential connection between the COVID-19 vaccine and diabetic ketoacidosis. Common symptoms include thirst, polydipsia, polyuria, palpitations, a lack of appetite, and weariness. In extremely rare clinical circumstances, a COVID-19 vaccine recipient may develop diabetes complications such as hyperglycemia and ketoacidosis. In these circumstances, routine clinical care has a successful track record. It is advised to give vaccine recipients who are vulnerable to problems, such as those with type 1 diabetes as an underlying illness, extra attention.

**Key Words:** Diabetes; COVID-19; Vaccine; Ketoacidosis; Effect

Joob B, Wiwanitkit V. COVID-19 vaccination and diabetic ketoacidosis. *World J Diabetes* 2023; In press

**Core Tip:** There has also been information on a potential connection between the coronavirus disease 2019 (COVID-19) vaccine and diabetic ketoacidosis. Common symptoms include thirst, polydipsia, polyuria, palpitations, a lack of appetite, and weariness. In extremely rare clinical circumstances, a COVID-19 vaccine recipient may develop diabetes complications such as hyperglycemia and ketoacidosis.

**INTRODUCTION**

Because of the pandemic's high transmission rate, an effective COVID-19 vaccine is urgently needed[1]. The available literature indicates that both vaccines help prevent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. However, given that the vaccination is new, any potential side effects are of greater concern[2–3]. When a handful of novel vaccines created in response to the COVID-19 pandemic got emergency approval and were widely distributed in late 2020[2], pharmacovigilance was unwittingly thrust into the spotlight. An effective global post marketing safety surveillance system was emphasized due to the employment of cutting-edge technologies and the anticipated rapid and widespread deployment of the vaccinations. The vaccinations went through extensive clinical evaluation and regulatory authority review. Many reports on the adverse effects of the COVID-19 vaccination have focused on how diverse they are. Clinical endocrinology is quite concerned about the endocrine issue that manifests after receiving the COVID-19 vaccination. The main concern expressed by the authors of this paper is that diabetes can become a medical problem after receiving the COVID-19 vaccine. After getting the COVID-19 vaccination, numerous clinical issues could arise, as was already mentioned. There are also some interesting reports regarding diabetes. The key words are provided here with a brief explanation.

Diabetes and COVID-19 have a well-established association. There is a bidirectional causal relationship between COVID-19 and type 2 diabetes. Diabetes may exacerbate COVID-19 severity, and COVID-19 vulnerability may increase diabetes risk[4]. Diabetes patients should receive the COVID-19 vaccine, just like everyone else, to protect themselves from the disease. It is critical to discuss the risks of vaccination for those who currently have diabetes mellitus. Piccini *et al*[5] evaluate the likelihood of glycemic control modification, insulin dose adjustment, and adverse effects following COVID-19 vaccination in young people with type 1 diabetes who use varying degrees of technology[5]. Piccini *et al*[5] came to the conclusion that receiving the OVID-19 immunization did not significantly increase the risk of glycemic control disturbance in type 1 diabetes adolescents and young adults[5]. This information may be helpful clinically[6] when counseling families about the SARS-CoV-2 vaccine for young people with type 1 diabetes. In a study by D'Addio *et al*[6] that investigated the immunogenicity and security of SARS-CoV-2 mRNA vaccines, a cohort of individuals with type 1 diabetes took part[5]. The vaccination demonstrated both dependability and security, according to D'Addio *et al*[6].

Several reports claim that COVID-19 vaccine recipients have problems with their diabetes. The exacerbation of hyperglycemia in people with type 2 diabetes after receiving the COVID-19 vaccination is the first problem that needs to be addressed[7]. Mishra *et al*[7] claim that an early inflammatory reaction to the vaccine and a subsequent immunological response are likely to be the causes of a minor and transient rise in blood sugar levels[7]. Mishra *et al*[7] published a case series that substantiated the etiology of transient immuno-inflammation because all episodes of hyperglycemia were self-limited and did not require significant treatment modifications[7]. A rapid jump in blood sugar levels appears to be caused by a vaccine. The possibility of a mild to moderate rise in blood sugar levels following vaccination has been theorized[7]. One patient experienced new-onset type 2 diabetes after receiving the COVID-19 vaccine, which is known as hyperosmolar hyperglycemia state[8].

**COVID-19 vaccination and diabetic ketoacidosis**

Clinical diabetology has an intriguing discussion regarding the COVID-19 vaccine and diabetic ketoacidosis. As was already indicated, the immunization may cause hyperviscosity and have unintended side effects. Additionally, reports of a connection between the COVID-19 immunization and diabetic ketoacidosis have been made. Three days after the first dose of COVID-19 RNA-based vaccines, the patient typically experiences thirst, polydipsia, polyuria, palpitations, a lack of appetite, and exhaustion without a prior history of diabetes[9]. Hyperglycemia, anion gap metabolic acidosis, and ketonuria are the three main signs of classic diabetic ketoacidosis[9]. It is possible to detect insulin autoantibody positivity and latent thyroid autoimmunity[10]. Ganakumar *et al*[11] advised that people with diabetes, particularly those with type 1 diabetes mellitus and inadequate glycemic control, be constantly monitored for hyperglycemia and ketonemia for at least two weeks after receiving the COVID-19 vaccine[11]. Autoimmunity and genetic predisposition may have contributed to the onset of the disease, even if the precise pathophysiologic mechanisms underlying type 1 diabetes are still unknown[12].

According to Tang *et al*[12], vaccination could result in type 1 diabetes, irreversible islet beta cell loss, and autoimmunity in persons with susceptible genetic backgrounds[12]. The problem might be more serious and more likely to occur in situations where type 1 diabetes is already present. Yakou *et al*[13] advised that the immunization be cautiously administered to type 1 diabetes patients receiving strict insulin therapy and a sodium-glucose transporter[13] due to the increased risk of ketoacidosis. In the affected case, despite hyperglycemia and diabetic ketoacidosis (DKA) after SARS-CoV-2 immunization, low glycohemoglobin levels are a crucial indicator of COVID-19 vaccine-related DKA[14]. As a preventive measure, it is essential to counsel patients to continue getting insulin injections[13]. Due to the significant risk of ketoacidosis, the vaccination should be cautiously given to type 1 diabetes patients receiving rigorous insulin therapy and a sodium-glucose transporter[15]. When a patient becomes ill, it's crucial to remind them to continue taking their insulin injections and to drink enough fluids[13]. A similar preventative concern should be used in the case of the patient with poorly controlled type 2 diabetes, in addition to the patient with underlying type 1 diabetes. According to Kshetree *et al*[15], Type I or dysglycemia in Type 2 diabetes mellitus is becoming more frequently documented following COVID-19 vaccinations or infection[16]. The mechanisms could be autoimmunity following mRNA vaccinations, cytokine-mediated beta-cell injury, or as a component of an autoimmune syndrome brought on by vaccine adjuvants[15]. Further investigation into the negative effects of people prone to life-threatening illnesses is required, as suggested by Lin *et al*[14]. Also, there might be a need for postvaccination surveillance on both hyperglycemia and DKA problems[16].

Concerning the reported cases of a link between COVID-19 vaccination and diabetes ketoacidosis, an important clinical question is whether ketosis in type 1 diabetes is related to the use of sodium-glucose transport protein 2 (SGLT2) inhibitors. The clinical history of the vaccine recipients in the published articles on the clinical association usually revealed no use of SGLT2 inhibitors, which could be a clue to support the possible clinical association between COVID-19 vaccination and ketoacidosis. Last but not least, it should be noted that the mRNA COVID-19 vaccine is primarily associated with most findings on the relationship between COVID-19 immunization and diabetic ketoacidosis. There are, however, a few reports of clinical associations with other vaccination types (viral vector and inactivated COVID-19 vaccines) that have been documented[11]. The fact that the mRNA vaccination is currently the primary recommended COVID-19 vaccine may be the cause of the higher number of reported cases in the mRNA vaccine group. As previously stated, the COVID-19 vaccination may cause diabetic ketoacidosis in patients with type 1 or type 2 diabetes mellitus (Table 1).

There are significant differences in COVD-19 vaccine-induced diabetes ketoacidosis between recipients with type 1 and type 2 diabetes. COVID-19 vaccine induced diabetes ketoacidosis usually occurs in adolescent male cases with inadequate glycemic control in cases with background type 1 diabetes mellitus[11]. This is the same pattern seen in diabetic ketoacidosis caused by COVID-19 in type 1 diabetes patients[17]. There are fewer reported cases of COVID-19 vaccine-induced diabetes ketoacidosis in people with type 2 diabetes mellitus, and the patient is usually an elderly man with a long history of diabetic illness[15]. The background hemoglobin A1C level, on the other hand, has not been identified as a risk factor for the development of COVID-19 vaccine-induced diabetic ketoacidosis[18].

**CONCLUSION**

In general, the COVID-19 immunization should be given to the diabetic patient because it has been proven to be effective. Generally, it has been confirmed that it is secure. In exceedingly uncommon clinical situations, a COVID-19 vaccination recipient may experience diabetes-related problems such as hyperglycemia and ketoacidosis. Routine clinical care has a history of success in some situations. Users of vaccines who are more likely to develop problems, such as those who already have type 1 diabetes as an underlying illness, are advised to receive additional attention. Because there is a possible link between the COVID vaccine and ketoacidosis, the risk diabetic case must be closely monitored. There is still a need for more clinical research on this subject because there isn't any *in vivo* or *in vitro* experimental data at this time.

**REFERENCES**

1 **Li YD**, Chi WY, Su JH, Ferrall L, Hung CF, Wu TC. Coronavirus vaccine development: from SARS and MERS to COVID-19. *J Biomed Sci* 2020; **27**: 104 [PMID: 33341119 DOI: 10.1186/s12929-020-00695-2]

2 **Meo SA**, Bukhari IA, Akram J, Meo AS, Klonoff DC. COVID-19 vaccines: comparison of biological, pharmacological characteristics and adverse effects of Pfizer/BioNTech and Moderna Vaccines. *Eur Rev Med Pharmacol Sci* 2021; **25**: 1663-1669 [PMID: 33629336 DOI: 10.26355/eurrev\_202102\_24877]

3 **Rudolph A**, Mitchell J, Barrett J, Sköld H, Taavola H, Erlanson N, Melgarejo-González C, Yue QY. Global safety monitoring of COVID-19 vaccines: how pharmacovigilance rose to the challenge. *Ther Adv Drug Saf* 2022; **13**: 20420986221118972 [PMID: 36052399 DOI: 10.1177/20420986221118972]

4 **Cao H**, Baranova A, Wei X, Wang C, Zhang F. Bidirectional causal associations between type 2 diabetes and COVID-19. *J Med Virol* 2023; **95**: e28100 [PMID: 36029131 DOI: 10.1002/jmv.28100]

5 **Piccini B**, Pessina B, Pezzoli F, Casalini E, Toni S. COVID-19 vaccination in adolescents and young adults with type 1 diabetes: Glycemic control and side effects. *Pediatr Diabetes* 2022; **23**: 469-472 [PMID: 35150596 DOI: 10.1111/pedi.13326]

6 **D'Addio F**, Sabiu G, Usuelli V, Assi E, Abdelsalam A, Maestroni A, Seelam AJ, Ben Nasr M, Loretelli C, Mileto D, Rossi G, Pastore I, Montefusco L, Morpurgo PS, Plebani L, Rossi A, Chebat E, Bolla AM, Lunati ME, Mameli C, Macedoni M, Antinori S, Rusconi S, Gallieni M, Berra C, Folli F, Galli M, Gismondo MR, Zuccotti G, Fiorina P. Immunogenicity and Safety of SARS-CoV-2 mRNA Vaccines in a Cohort of Patients With Type 1 Diabetes. *Diabetes* 2022; **71**: 1800-1806 [PMID: 35551366 DOI: 10.2337/db22-0053]

7 **Mishra A**, Ghosh A, Dutta K, Tyagi K, Misra A. Exacerbation of hyperglycemia in patients with type 2 diabetes after vaccination for COVID19: Report of three cases. *Diabetes Metab Syndr* 2021; **15**: 102151 [PMID: 34186339 DOI: 10.1016/j.dsx.2021.05.024]

8 **Abu-Rumaileh MA**, Gharaibeh AM, Gharaibeh NE. COVID-19 Vaccine and Hyperosmolar Hyperglycemic State. *Cureus* 2021; **13**: e14125 [PMID: 33927933 DOI: 10.7759/cureus.14125]

9 **Sakurai K**, Narita D, Saito N, Ueno T, Sato R, Niitsuma S, Takahashi K, Arihara Z. Type 1 diabetes mellitus following COVID-19 RNA-based vaccine. *J Diabetes Investig* 2022; **13**: 1290-1292 [PMID: 35220662 DOI: 10.1111/jdi.13781]

10 **Yano M**, Morioka T, Natsuki Y, Sasaki K, Kakutani Y, Ochi A, Yamazaki Y, Shoji T, Emoto M. New-onset Type 1 Diabetes after COVID-19 mRNA Vaccination. *Intern Med* 2022; **61**: 1197-1200 [PMID: 35135929 DOI: 10.2169/internalmedicine.9004-21]

11 **Ganakumar V**, Jethwani P, Roy A, Shukla R, Mittal M, Garg MK. Diabetic ketoacidosis (DKA) in type 1 diabetes mellitus (T1DM) temporally related to COVID-19 vaccination. *Diabetes Metab Syndr* 2022; **16**: 102371 [PMID: 34954484 DOI: 10.1016/j.dsx.2021.102371]

12 **Tang X**, He B, Liu Z, Zhou Z, Li X. Fulminant type 1 diabetes after COVID-19 vaccination. *Diabetes Metab* 2022; **48**: 101324 [PMID: 35091092 DOI: 10.1016/j.diabet.2022.101324]

13 **Yakou F**, Saburi M, Hirose A, Akaoka H, Hirota Y, Kobayashi T, Awane N, Asahi N, Amagawa T, Ozawa S, Ohno A, Matsushita T. A Case Series of Ketoacidosis After Coronavirus Disease 2019 Vaccination in Patients With Type 1 Diabetes. *Front Endocrinol (Lausanne)* 2022; **13**: 840580 [PMID: 35370952 DOI: 10.3389/fendo.2022.840580]

14 **Lin R**, Lin YW, Chen MH. Fulminant Type 1 Diabetes Mellitus after SARS-CoV-2 Vaccination: A Case Report. *Vaccines (Basel)* 2022; **10** [PMID: 36423001 DOI: 10.3390/vaccines10111905]

15 **Kshetree B**, Lee J, Acharya S. COVID-19 Vaccine-Induced Rapid Progression of Prediabetes to Ketosis-Prone Diabetes Mellitus in an Elderly Male. *Cureus* 2022; **14**: e28830 [PMID: 36225440 DOI: 10.7759/cureus.28830]

16 **Samuel SM**, Varghese E, Triggle CR, Büsselberg D. COVID-19 Vaccines and Hyperglycemia-Is There a Need for Postvaccination Surveillance? *Vaccines (Basel)* 2022; **10** [PMID: 35335086 DOI: 10.3390/vaccines10030454]

17 **Kountouri A**, Korakas E, Ikonomidis I, Raptis A, Tentolouris N, Dimitriadis G, Lambadiari V. Type 1 Diabetes Mellitus in the SARS-CoV-2 Pandemic: Oxidative Stress as a Major Pathophysiological Mechanism Linked to Adverse Clinical Outcomes. *Antioxidants (Basel)*. 2021; **10**: 752 [PMID: 34065123 DOI: 10.3390/antiox10050752]

18 **Wan EYF**, Chui CSL, Mok AHY, Xu W, Yan VKC, Lai FTT, Li X, Wong CKH, Chan EWY, Lui DTW, Tan KCB, Hung IFN, Lam CLK, Leung GM, Wong ICK. mRNA (BNT162b2) and Inactivated (CoronaVac) COVID-19 Vaccination and Risk of Adverse Events and Acute Diabetic Complications in Patients with Type 2 Diabetes Mellitus: A Population-Based Study. *Drug Saf.* 2022; 45: 1477-1490 [PMID: 36184720 DOI: 10.1007/s40264-022-01228-6]

**Footnotes**

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

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

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

**Peer-review model:** Single blind

**Peer-review started:** December 15, 2022

**First decision:** January 17, 2023

**Article in press:**

**Specialty type:** Endocrinology and metabolism

**Country/Territory of origin:** Thailand

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): B

Grade C (Good): C, C, C

Grade D (Fair): D

Grade E (Poor): 0

**P-Reviewer:** Cai L, United States; Dong Z, China; Moreno-Gómez-Toledano R, Spain; Wu QN, China; Zhang F, China **S-Editor:** Li L **L-Editor:** A **P-Editor:**

**Table 1 Table summarizing the key information of coronavirus disease-19 vaccine related diabetic ketoacidosis in recipients with background type 1 and type 2 diabetes mellitus**

|  |  |  |
| --- | --- | --- |
| **Characteristics** | **Cases with background type 1 diabetes mellitus** | **Cases with background type 2 diabetes mellitus** |
| Sex | Usually male | Usually male |
| Age group | Adolescent | Elderly |
| Background diabetes control | Poor control | No significant relationship |
| During of diabetic illness | Long | No significant relationship |