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COMMENTARY

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Third dose of COVID-19 vaccine in diabetes: Relevance of good metabolic control to improve its efficacy

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Coronavirus (COVID-19) disease is usually characterised by poor prognosis in patients with diabetes implying that mitigation of the COVID-19 pandemic risk becomes a priority in patients with type 1 (T1D) or type 2 (T2D) diabetes.[1] Despite that COVID-19 vaccination represents the most powerful tool to mitigate COVID-19 disease, multiple unresolved issues with regard to the efficacy and durability of COVID-19 vaccine in patients with diabetes still remain unsolved.

A recent systematic review summarises the main evidence of vaccine safety and effectiveness in adult patients with diabetes.[2] The authors underline that, although age was one of the most influencing factors in COVID-19 immune response to the vaccine, older people with diabetes showed even lower antibody response compared to people in the same age group without diabetes. However, this reduced effect of vaccine in patients with diabetes was minimised when they were vaccinated at the time of good glycaemic control.[2]

This topic rises as central in the vaccination efforts against SARS-Cov-2 in diabetes. The few studies conducted until now point out the impaired immune response towards SARS-Cov-2 vaccination in affected patients. Interestingly, a recent study highlighted the presence of lower antibody response to COVID-19 vaccination both in T1D and T2D.[3] However, given the fact that persistent hyperglycaemia seems to worsen patients' prognosis to COVID-19,[4] the question arises whether the poor glycaemic control may be correlated to the level of antibody response and to the ensuing protection after COVID-19 vaccination.

In a study conducted to assess the immune response after BNT162b2 vaccine in 374 Japanese health workers, after univariate and multivariate regression analysis, HbA1c $\geq$ 6.5% was associated with a lower immune response.[5] A recent observational Italian study (CAVEAT study) demonstrated a lower antibody response after 21 days from the second vaccination in T2D subjects with poor glycaemic control (glycated haemoglobin HbA1c > 7%).[6] This result was accompanied by reduced CD4-positive T cell response evaluated by measuring tumour necrosis factor (TNF)-α, interleukin (IL)-2, or interferon (IFN)-γ response. Interestingly, the same study also showed that reduction of HbA1c on day 52 after vaccination was associated with an increase in neutralising antibody titres and CD4 T-cell cytokines, implying that optimization of glycaemic control during the post-vaccination period improves the immunological response in this population.

The observation that presence of hyperglycaemia at the time of vaccination worsens the immunological response to COVID-19 vaccine, and that individuals with T2D initially poorly controlled, improved their immune responses when achieving recommended glycaemic targets, indicates that metabolic control around the time of vaccination period can play a pivotal role for successful protection in patients with diabetes.

Other than the impact of glucose control, an impairment in cellular immune response could also have an effect on the impaired COVID-19 vaccine response in people with diabetes. Data from nursing homes' residents in Belgium showed that the presence of diabetes was associated with lower cellular immunogenicity as measured by secretion of IFN-γ.[7] On the other side, reduction of blood glucose following a restriction in caloric intake in obese subjects correlates with increased IFN-γ.[8]

Concerns also exist about vaccine-induced dysglycaemia among people with T1D and T2D. Thus, pro-inflammatory cytokines resulting from vaccination may reduce insulin sensitivity, potentially deteriorating glucose control.[9]

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Further studies are urgently needed to investigate the efficacy of SARS-Cov-2 vaccination in people with diabetes with the major focus on the improvement of glycaemic control to potentiate the vaccine effect.

Although data with regard to glycaemic control in response to COVID-19 immunisation are still limited, a recent sub-study of the COVAC-DM (*Immune Response to COVID-19 Vaccination in People with Diabetes Mellitus Study*) made some interesting observations. Following COVID-19 vaccination, glycaemic parameters assessed by continuous glucose monitoring (CGM) both in T1D and T2D patients did not change. More recently, no significant differences in glucose control were also observed in patients with autoimmune diabetes, expressed as time in range evaluated by CGM comparing the 3 days after SARS-Cov-2 vaccine with the 14 days preceding the vaccine.[10] Nonetheless, deterioration in glycaemia was still observed in people with T1D when side effects were reported following the administration of COVID-19 vaccine.[11]

While this observation should be further investigated in larger studies, health care professionals should immediately consider potential glycaemic aberrations in response to COVID-19 immunisation, and thus intensify glucose monitoring within the weeks before and after vaccination.

A direct mechanism evidence of the immune cell metabolic impairment by hyperglycaemia comes from an in vitro study showing that changes in glucose concentrations in culture media impair the expression of intracellular glucose transporters in B and T lymphocytes, the immune effectors that relate to the humoral and cellular immune responses, respectively.[12] Not surprisingly, B and T lymphocyte cell-intrinsic changes have been identified in individuals with T2D.[13]

In view of vaccine-induced hyperglycaemia,[14] early evaluation and screening of patients with glycaemic impairment, following COVID-19 vaccination is recommended.

Glucose managing technologies such as “continuous” and “flash” monitoring systems (CGM, FGM) have been shown to improve glycaemic control and to reduce glucose variability in patients with T1D and T2D.[15] These technologies could help diabetologists to optimise diabetes therapy with the aim to improve metabolic control in preparation for vaccine administration.[16]

In this perspective, the short-term use of CGM or FGM devices on the occasion of the third dose of COVID-19 vaccine's administration may represent a cost-effective option for disease management in patients with diabetes.

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CONFLICT OF INTEREST

The authors declare no conflict of interest pertinent to the present commentary.

ETHICS STATEMENT

All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

AUTHOR CONTRIBUTIONS

Silvia Pieralice and Luca D’Onofrio - conceptualisation, writing, review and editing of the manuscript; Raffaella Buzzetti and Paolo Pozzilli - conceptual guidance, critical revision and editing of the manuscript. All authors read, commented, and approved the final version of the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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