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Immune Response to COVID-19 Vaccine in People with Type 1 Diabetes. A Monocentric Prospective Evaluation

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Abstract

People with DM have been described to show alterations in immune system, with a potential increased susceptibility to infections. Moreover, univocal and clear data about a potential role of these alterations on immune response to vaccines, in particular to COVID-19, are not available. In this study, we aimed at quantify the extent of the immunologic response and the duration of protection in the first 52 weeks after the administration of the mRNA vaccine against SARS-CoV-2, according to the national vaccination plan in individuals with type 1 DM.

133 individuals (76 F/57M) were enrolled in this study. Anti-S antibody levels was assessed before and 1, 3, 6 and 12 months after the second vaccine dose. Our study demonstrated that patients with type 1 DM display an adequate humoral immune response to COVID-19 vaccination, with a prompt and effective antibody production from the first month after the first two doses (Anti-S antibody 2±13 to 5171±3462 to 2530±1948 to 2697±3151 to 5997±3899, respectively before and 1, 3, 6 and 12 months after second dose of vaccine). We did not find different time patterns of Anti-S1 levels according to glucose control, gender, age class, and BMI category. In conclusion, the findings obtained from our study group reinforce the evidence of the effectiveness of COVID-19 vaccination in people with type 1 diabetes, as well as in the general population.

Keywords: COVID-19; Type 1 Diabetes; Vaccine.

Article Highlights

- We undertook this study to reinforce the evidence of the effectiveness of the covid-19 vaccine in subjects with type 1 diabetes
- In particular, we wanted to demonstrate that, in subjects with type 1 diabetes, the first antibody production and the trend of humoral response over time to COVID-19 vaccine was similar to general population
- Our study demonstrated that patients with type 1 DM display an adequate humoral immune response to COVID-19 vaccination.
- Our findings further strengthen the evidence that people with type 1 diabetes should join the vaccination campaign against SARS-CoV-2, as general population.

Introduction

According to data released by the World Health Organization (WHO) in January 2024, COronaVIrus Disease 19 (COVID-19) has caused worldwide more than 750 million infections and more than 7,000,000 deaths [1]. COVID 19 is the third epidemic caused by a new Coronavirus after the Severe Acute Respiratory Syndrome (SARS), which developed in Hong Kong in the early 2000s [2] and the Middle East Respiratory Syndrome (MERS), which spread in 2012 in the Arabian Peninsula [3]. Although there are many characteristics in common with SARS, the viral particles of SARS-CoV-2 are eliminated by the host during the pre-symptomatic phase of the infection, making the prevention of the virus spread a real burden [4]. At the beginning of epidemic, the rapid and global propagation of the infection has had a disastrous impact on global healthcare systems, considering that 20% of infected patients showed severe clinical manifestation with hypoxia and the need for respiratory support, 5% suffered from Acute Respiratory Distress Syndrome (ARDS) and that the mortality risk was 2.3% [5].

Regarding diabetes mellitus (DM) and COVID-19, several studies demonstrated that people with DM showed an increased risk of SARS-CoV-2 infection, development of complications, and admission to intensive care, prolonged hospitalization and mortality during hospitalization [6–9]. However, most of the currently available studies have been carried out on people with Type 2 DM. Data on type 1 DM are far less exhaustive but, however, they suggest an increased risk of mortality during hospitalization of these population if compared to non-diabetic individuals [10], identifying poor glycometabolic control [11], the presence of cardio-renal complications, a poor social context and the lack of technology use as risk factors [12]. The efforts of the scientific community have focused on developing effective vaccines, capable of limiting the spread of the virus among the global population. Immunogenicity is specifically guaranteed by the generation of neutralizing antibodies against the Spike Protein (SP- a virus membrane antigen), which have therefore been identified as biomarker of protection and effectiveness of the immune response [13].

The kinetics of the production of anti-Spike antibodies have been well described, with a prompt seroconversion of IgM occurring in ten days from exposure to the virus (with rapid decline in 18 days) and of IgG in 3 weeks with a subsequent decline starting from the following 8 weeks [14]. Data from literature suggest that both the cellular immune response (in particular T-helper 1 mediated), and the humoral immune response contribute to adequate antibody production in reaction to the infection or the antigenic stimulus provided with the vaccine [15,16]. People with DM have been described to show alterations in both acquired and innate humoral and cell-mediated immunity, with a potential increased susceptibility to infections [17]. However, it has not yet been univocally defined whether and how these alterations may affect the immune response to vaccines. A recent review by Verstraeten T. et al [18] demonstrated a reduced antibody response in subjects with DM to anti-HBV vaccination, while data on vaccines for influenza virus and pneumococcus are still conflicting.

In this context, the limited data regarding the subpopulation with type 1 DM are even less conclusive. In particular, data from three studies on children, adolescents [19,20] and adults with long-lasting disease [21] showed a reduced antibody production following the standard HBV vaccination protocol, while this appears comparable to the healthy population in a study on young diabetics performed in 1996 [22]. The only long-term follow-up study actually available shows an adequate persistence of the antibody titer in responders [23]. Again, the only work concerning the response to influenza vaccine with a distinction between people with type 2 and 1 DM, demonstrated that paradoxically the latter population had a lower response than general population [24]. Finally, in 2002 Eibl N. et al demonstrated an in vitro and in vivo reduced T cell-mediated immune response in people with type 1 DM, which showed a significantly reduced response to vaccines carried out with T-dependent antigens (anti HAV and diphtheria toxoid), and a preserved response to the pneumococcal polysaccharide T-independent antigen. In particular, the response to the HAV vaccine remained lower than in general population with the first and second administration, reaching comparable levels only at the third dose [25].

The vaccination campaign against SARS-CoV-2 began in Italy on 27 December 2020. People with type 1 DM have been identified as part of the priority categories for the administration of the SARS-CoV-2 vaccine since the drafting of the vaccination plan published in the “Gazzetta Ufficiale della Repubblica Italiana” on 24 March

2021, as "extremely vulnerable" individuals [26]. The significant effectiveness of mRNA vaccines in reducing the development of severe disease from SARS-CoV-2 infection in the general population has been widely demonstrated [27,28]. Regarding to the extent and duration of antibody response to SARS-CoV-2 infection in diabetic patients, some short-term follow up studies showed a persistence of anti-Sars Cov2 antibodies after vaccine in people with DM (with no distinction between type 1 or 2 DM), with a response comparable to a control group of non-diabetic individuals [29]. To date, however, exhaustive evidences about a potential defect in the immune response to SARS-CoV-2 vaccine in people with type 1 DM are still lacking.

Aim of the Study

To quantify the extent of the immunologic response and the duration of protection in the first 52 weeks after the administration of the mRNA vaccine against SARS-CoV-2 according to the national vaccination plan in individuals with type 1 DM.

Methods

Study design: We conducted a monocentric, prospective, cohort study including adult (>18 years) individuals with type 1 DM. Study design is reported in Figure 1.

Participants: From March 2021 to April 2021, subjects with type 1 DM followed at the Diabetology Unit of Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico of Milano were screened for inclusion and agreed to participate in the study protocol.

Inclusion criteria were: diagnosis of type 1 DM, concomitant insulin treatment, HbA1c≥5%, agreement to be vaccinated for COVID-19 according to the vaccination schedule, written informed consensus obtained.

Exclusion criteria were: pregnancy, previous clinically manifest SARS-CoV-2 infection.

Methods

At screening, patients underwent an anthropometric evaluation and had a blood sample taken for determination of antibodies titer. Anti-SARS-CoV-2 nucleocapsid antibodies-total Ig and anti-SARS-CoV-2 spike RBD-total Ig were measured using Roche kits: Elecsys anti-SARS-CoV-2 and Elecsys anti-SARS-CoV-2 S respectively, on Roche Cobas e801-Roche Diagnostics, Monza Italy). Both tests are based on ElectroChemiLuminescent Immuno Assay (ECLIA). At baseline, also fasting glycaemia (mg/dl, hexokinase) and HbA1c (mmol/mol, HPLC), lipid profile (total cholesterol, CHOD-PAP, mg/dl, HDL cholesterol, mg/dl, tryglicerides GPO-PAP, mg/dl) and renal function (creatinine, Jaffe, mg/dl, calculation of glomerular filtration rate – GFR- according to CKD-EPI formula30) were measured. Anthropometric assessments were performed by measuring weight and height. Body mass index (BMI) was calculated as weight (kg)/ height ^{2} (m^2). Baseline demographic and clinical characteristics, including sex, age, insulin therapeutic scheme (i.e. multiple daily injection, MDI, or continuous subcutaneous insulin infusion, CSII scheme) and daily insulin requirements (IU/kg of body weight/ day) were recorded. The CSII therapy device was chosen during previous outpatient visits according to standard of care (Medtronic MiniMed 780G, Minneapolis, MN, USA; Tandem T:slim X2, San Diego, CA, USA; Roche Accu Chek Insight, Basel, CH; Roche Accu Chek Solo, Basel, CH; Insulet Omnipod, Acton, MA, USA; Ypsomed Ypsopump, Burgdorf, CH).

At screening, patients already wore an FGM/CGM system (Abbott Freestyle Libre 1, Chicago, IL, USA; Abbott Freestyle Libre 2, Chicago, IL, USA; Dexcom G4, San Diego, CA, USA; Dexcom G5, San Diego, CA, USA; Dexcom G6, San Diego, CA, USA; Medtronic Guardian 3, Minneapolis, MN, USA) according to standard of care.

After enrollment, all people received the first two doses of Spikevax - Moderna mRNA-1273 anti COVID-19 vaccine, according to the national vaccination plan. Follow up visits were performed 1, 3 and 6 months after the second vaccine dose and, at each visit, people had a blood sample taken for Anti-S1 antibody levels (U/ mL). The maximum level reported by the laboratory was 12,500 U mL. Six months after dose two, the third dose of Spikevax - Moderna mRNA-1273 anti COVID-19 vaccine was administered to all patients.

At end of trial visit, 12 months after the second vaccine dose, Anti-S1 antibody levels were measured.

The study complies with the Declaration of Helsinki. The research protocol was approved by the Ethics Committee of the IRCCS Ca' Granda – Ospedale Maggiore Policlinico Foundation. A written informed consent was provided by each participant.

Study Outcomes

The primary outcome was the change from baseline in Anti-S1 antibody levels, while possible differences in Anti-S1 antibody levels according to glycometabolic control (HbA1c ≥ or < 8 %, 64 mmol/mol) were considered as secondary outcomes.

Statistical Analysis

We calculated descriptive statistics for all participants. Conversely, since SARS-CoV-2 infection induces immune response with production of Anti-S1 and Anti-N antibodies, to have a cleaner picture of Anti-S1 levels over time we excluded from analysis samples in which the Anti-N level was increased (>=1 U/mL, indicating previous SARS-CoV-2 infection). We provide detailed descriptive statistics on anti-S1 antibody levels (min-max, first and third quartile, median, mean, and SD). To analyze the time pattern of anti-S1 levels stratified by gender, age class (<30, 30-44, and

>=45 years), BMI category (<25 and >=25 kg/m2), and glucose control (no/yes) we fitted random intercept regression models containing the covariate time (dummy variable) and interaction (product) terms between those variables and time; the product terms were then tested together using a global Wald test. Since in general anti-S1 levels have a log-normal distribution, in the regression models they were ln-transformed. Statistical analysis was performed with Stata 18 (StataCorp. 2023).

Results

Overall, 133 individuals (mean age: 48.0 ±2.8 years, 76 females, according to SAGER guidelines31) were enrolled in this study (Table 1- demographic and clinical characteristics). Table 2 provides their biochemical, anthropometric characteristics and the ambulatory glucose profile (AGP) metrics downloaded from their FGM/CGM devices. At baseline, 83 individuals (62.4%) were in MDI insulin therapy, while 50 individuals (37.6%) were on CSII therapy. Twenty-eight participants (21%) suffered from at least 1 micro or macrovascular complication of diabetes: 5 individuals (3.8%) had microalbuminuria, 1 (0.8%) had macroalbuminuria, 24 (18%) had retinopathy, 6 (4.5%) had cardio-vascular disease. Thirty-one participants (23%) suffered from at least 1 autoimmune disease out of type 1 diabetes (18 individuals with Hashimoto disease, 11 with Graves-Basedow disease, 8 with celiac disease, 1 with dermatomyositis, 4 with vitiligo, 2 with rheumatoid arthritis, 2 with autoimmune gastritis). At baseline, average Body Mass Index (BMI) of people participating in the study was in the normal range, according to world health organization (WHO) guidelines32, but glucose levels, HBA1c, coefficient of variation (CV), glucose management indicator (GMI) and time in range (TIR) were not within the target, according to ADA guidelines 202332. At baseline, anti-S1 anti-N levels were obtained from 127 patients. Of these, 16 had anti-N levels >= 1 U/mL and were therefore excluded. Among the 111 patients (samples) with negative (< 1 U/mL) anti-N antibody level, we observed, as expected, a marked increase of median anti-S1 antibody levels one month after the second vaccine dose (Table 3 and Figure 2). Only 2 female subjects with autoimmune diseases, not requiring immune-suppressive therapy (Basedow and Hashimoto disease), showed a very weak response (Anti-S1 between 10 and 25 U/mL). Only one male subject was a non-responder (Anti-S1<0.8 U/mL, the threshold for positivity). He was affected by polyglandular autoimmune (PGA) syndrome type III, Hashimoto disease, and dermatomyositis, and was in therapy with cyclosporine and mycophenolate mofetil (MMF). Median anti-S1 levels were 48% (2203/4598) lower after 3 months and 35% (1632/4598) lower after 6 months. At 12 months levels were again increased because most patients received the third vaccine dose.

When we stratified individuals according to glucose control (HbA1c < or ≥ 8%-64 mmol/mol) we observed similar patterns (P-value for interaction = 0.31) (Table 4). Subjects with uncontrolled diabetes had slightly lower median and mean anti-S1 levels than those with compensated diabetes at 3 and 6 months after the second vaccine dose. Conversely, they showed moderately higher levels at 12 months.Similarly, we did not find different time patterns of Anti-S1 levels according to gender, age class, and BMI category (P-values for interaction 0.86, 0.51, and 0.72, respectively).

	N.	%
ALL SUBJECTS	133	
GENDER		
Females	76	57.1
Males	57	42.9
AGE (years)		
<30	28	21.0
30-44	49	36.9
>=45	56	42.1
INJECTION DEVICE		
Multiple Daily Injections (MDI)	83	62.4
Insulin Pump/Patch Pump	50	37.6
CHRONIC COMPLICATIONS		
Microalbuminuria	5	3.8
Macroalbuminuria	1	0.8
Retinopathy	24	18.0
Cardio-vascular Disease	6	4.5
OTHER AUTOIMMUNITIES	31	23.3

Table 1: Demographics and clinical characteristics of T1DM (type 1 diabetes mellitus) individuals.

BIOCHEMICAL PARAMETERS	MEDIAN±SD
Glycemia (mg/dL)	154.1±66.1
HbA1c (%; mmol/mol)	7.4±1.4
Total cholesterol (mg/dL)	185.1±37.8
HDL cholesterol(mg/dL)	63.0±14.8
Tryglicerides(mg/dL)	83.6±59.2
LDL-cholsterol(mg/dL)	104.1±32.1
Creatinine(mg/dL)	0.8±0.2
cGFR (CKD-EPI formula)	100.2±18.6
ANTHROPOMETRIC PARAMETERS	
Weight (kg)	70.0±13.0
BMI (kg/m^2)	24.2±3.9
GLUCOSE CONTROL METRICS	
? glucose (mg/dL)	158.5±38.9
Coefficient of variation	36.4±9.3
Glucose management indicator	7.1±0.9
Time in range (%)	62.8±18.0
Time above range (%)	31.2±19.1
Time below range (%)	6.0±6.6

Table 2: Biochemical, anthropometric parameters and glucose-control metrics of 133 T1DM individuals.

Months after dose 2	N samples	Min	First quartile	Median	Mean	Third quartile	Max*	SD
0	111	0	0	0	2	0	126	13
1	111	0	2353	4598	5171	7649	12500	3462
3	85	3	1032	2203	2530	3361	10393	1948
6	67	229	788	1632	2697	2863	12500	3151
12	31	1021	2621	5546	5997	9205	12500	3899
*Maximum level reported by the laboratory: 12,500 U/mL.								

Table 3: Anti-S1 antibody levels (U/mL) in T1DM samples with negative anti-N levels (< 1 U/mL).

Months after dose 2	N	Min	First quartile	Median	Mean	Third quartile	Max	SD
Compensated diabetes (HbA1c <8%, 64mm/mol)								
0	44	0	0	0	4	0	126	19
3	24	309	1548	2584	2772	3564	8404	1903
6	25	229	1436	1768	2635	2673	12500	2595
12	14	1021	2208	3858	4881	5798	12500	3538
Uncontrolled diabetes (HbA1c ≥8%, 64mm/mol)								
0	50	0	0	0	0	0	3	0
3	25	271	993	1926	2376	2683	10393	2281
6	27	255	788	1503	3199	3265	12500	4090
12	11	1200	3847	5746	7242	12500	12500	4043

Table 4: Anti-S1 antibody levels (U/mL) in T1DM samples with negative anti-N levels (< 1 U/mL), according to glucose control.

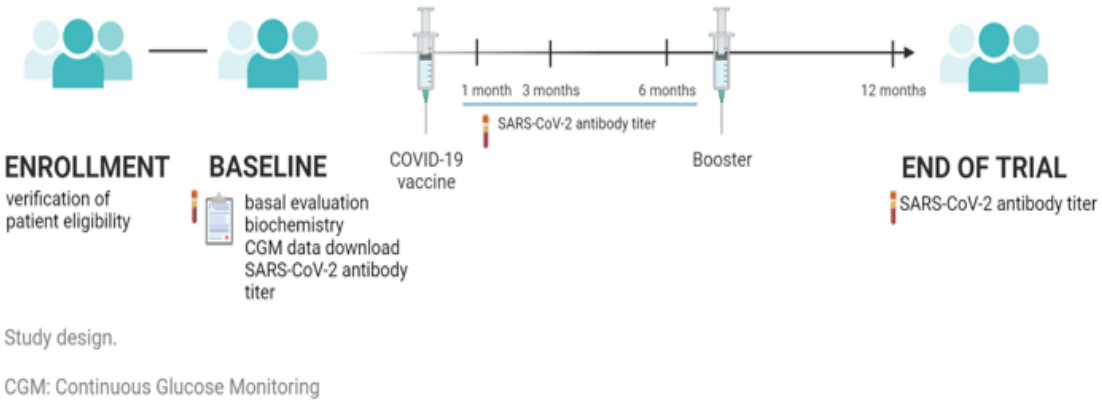

Figure 1: Study design.

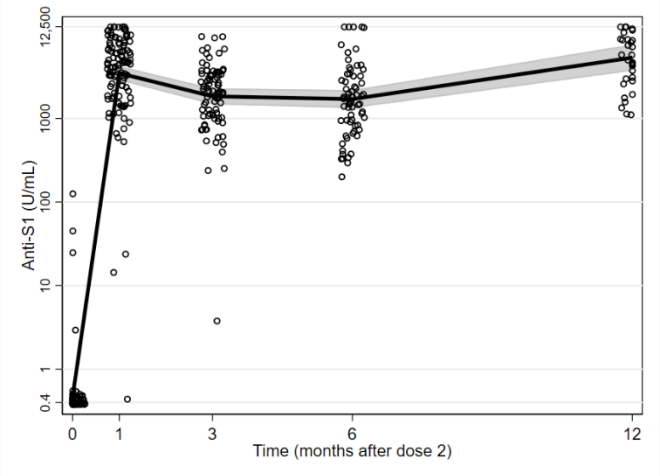

Figure 2: Anti-S1 antibody levels (U/mL) in T1DM patients from baseline to end of trial visit.

Discussion

With the availability of COVID-19 vaccines, the prioritization of groups of individuals to receive immunization has become a crucial challenge [34].Actually, a greater morbidity and mortality from COVID-19 in people with diabetes has been widely demonstrated, but most of this information comes from individuals with type 2 DM, with less knowledge about the risk in type 1 DM, and experts have cautioned against extrapolating conclusion on people with type 1 diabetes from studies conducted in populations composed by people with type 2 diabetes [35]. Although the Centers for Disease Control and Prevention (CDC) currently categorize people with type 2 DM at higher risk for severe complications from COVID-19 than people with type 1 DM [36], several recent studies showed that people with both type 1 or type 2 diabetes have an increased vulnerability to serious illness from the infection [10,12,37].

As mentioned before, it has been supposed that people with DM could show alterations in both humoral and cell-mediated immunity [17], without evidence on a possible negative effect on immune response to vaccines. In this context, the limited data regarding the subpopulation with type 1 DM are even less conclusive and, actually, no data are available on potential defects in the humoral response to COVID-19 vaccination in people with type 1 diabetes.

Recently, D'Onofrio et al demonstrated a reduced early response to vaccination in people with type 1 and 2 DM, with decreased levels of specific antibodies after one month compared to controls, even after correction for age and gender, and no difference was found between subjects with type 1 and type 2 diabetes [38]. Concerning short-term safety, in a subgroup analysis from the global COVAD

study, Chatterjee et al. demonstrated that COVID-19 vaccination was safe and well tolerated in people with type 1 diabetes with similar AE profiles compared with healthy controls, although severe rashes were more common in type 1 diabetes individuals [39].

Our study demonstrated that patients with type 1 DM display an adequate humoral immune response to COVID-19 vaccination, with a prompt and effective antibody production from the first month after the first two doses. Regarding the relationship between glucose control and response to vaccination, previous studies suggested a link between HbA1c levels and cellular and humoral responses [40]. In particular, in a study conducted by Mitsunaga et al., type 2 diabetes was associated with a reduced level of anti-spikeAb, andHbA1c>6.5% further impaired the immune response [41]. Also in the CAVEAT study, a HbA1c>7% was related to a worse response to the vaccine 21 days after the second vaccine administration in patients with type 2 diabetes [42].

Our findings are in line with the results from the COVAC-DM study43, where no relationship was demonstrated between glycemic control antibody response to COVID-19 vaccination. The same findings were reported in the study conducted by d'Onofrio et al [38], in which the authors didn't find any correlation between HbA1c levels and Ab production.

Finally, in our study, the first antibody production and the trend of humoral response over time was similar to that observed in a large cohort of (mostly healthy) healthcare workers of Fondazione IRCCS Ca' Granda Ospedale Maggiore– Policlinico Hospital, Milan, with similar demographics [29].

In conclusion, the findings obtained from our study group reinforce the evidence of the effectiveness of COVID-19 vaccination in people with type 1 diabetes, as well as in the general population.

Strengths and limitations

To our knowledge this is the first study to investigate the effectiveness of COVID-19 vaccination focusing on a population composed solely by individuals with type 1 diabetes. The main limitation was the low number of samples available at 6 and 12 months.

Author Contributions: V.G., A.M. and L.L.P. conceptualized and designed the study, drafted the manuscript and collect-ed data. D.C. Carried out the statistical analyses and critically reviewed the manuscript. V.R., I.C., A.G., F.C., G.M., E.F. and Y.P. collected data. E.O. and A.B. coordinated and supervised data collection, and critically reviewed the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work. V.G. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Conflict of Interest: Authors didn't report any conflict of interest

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