Immunogenicity and Safety of SARS-CoV-2 mRNA Vaccines in a Cohort of Patients With Type 1 Diabetes

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Patients with type 1 diabetes (T1D) may develop severe outcomes during coronavirus disease 2019 (COVID-19), but their ability to generate an immune response against the SARS-CoV-2 mRNA vaccines remains to be established. We evaluated the safety, immunogenicity, and glycometabolic effects of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) mRNA vaccines in patients with T1D. A total of 375 patients (326 with T1D and 49 subjects without diabetes) who received two doses of the SARS-CoV-2 mRNA vaccines (mRNA-1273, BNT162b2) between March and April 2021 at ASST Fatebenefratelli Sacco were included in this monocentric observational study. Local and systemic adverse events were reported in both groups after SARS-CoV-2 mRNA vaccination, without statistical differences between them. While both patients with T1D and subjects without diabetes exhibited a parallel increase in anti-SARS-CoV-2 spike titers after vaccination, the majority of patients with T1D (70% and 78%, respectively) did not show any increase in the SARS-CoV-2–specific cytotoxic response compared with the robust increase observed in all subjects without diabetes. A reduced secretion of the T-cell–related cytokines interleukin-2 and tumor necrosis factor-α in vaccinated patients with T1D was also observed. No glycometabolic alterations were evident in patients with T1D using continuous glucose monitoring during follow-up. Administration of the SARS-CoV-2 mRNA vaccine is associated with an impaired cellular SARS-CoV-2–specific cytotoxic immune response in patients with T1D.

Patients affected by both type 1 diabetes (T1D) and type 2 diabetes may develop more severe outcomes during severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (1,2), and glycometabolic control is altered during coronavirus disease 2019 (COVID-19) (3,4).

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The recent availability of novel vaccines against SARS-CoV-2 (5) suggests that primary prevention based on vaccination may be a key strategy to dampen the risks associated with COVID-19 in patients with T1D. Because an impaired humoral/cellular immune response to vaccination was hypothesized in patients with diabetes (6–8), careful consideration of age and timing of disease onset has been proposed when considering vaccination for patients with T1D. While benefits are known for common vaccinations, the use of novel vaccines, such as that for SARS-CoV-2, may be challenging (8–10). Given the more severe outcomes during SARS-CoV-2 infection (11), patients with T1D should be a priority group to receive the COVID-19 vaccine (12), although studies in this population are lacking (13). In the current study, we assessed the safety, immunogenicity, and glycometabolic effects of the SARS-CoV-2 mRNA vaccines in patients with T1D and provide new evidence for an impaired SARS-CoV-2–specific cellular cytotoxic immune response in patients with T1D.

RESEARCH DESIGN AND METHODS

Study Design and Participants

This monocentric observational study was conducted at the Endocrinology and Diabetology Unit, ASST Fatebenefratelli Sacco in Milan, Italy, according to the principles of the Declaration of Helsinki, and the protocol was approved by the Comitato Etico Milano Area 1 (Effect of SARS-CoV-2 [COVID-19] Vaccination in Type 1 Diabetes [CoVaxT1D]). A total of 375 subjects (326 patients with T1D and 49 subjects without diabetes [frail patients without diabetes as defined on the basis of guidelines issued by the Italian Ministry of Health and caregivers/family members of patients with T1D) (Table 1) received two doses of SARS-CoV-2 mRNA vaccines (Supplementary Table 1) between 26 March and 18 April 2021 and signed informed consent (Supplementary Fig. 1). Patients with active COVID-19 or a diagnosis of COVID-19 within the previous 3 months were excluded. The primary outcomes of the current study were the safety of the mRNA vaccines in patients with T1D, as measured by report of local/systemic adverse events; humoral immunogenicity, as measured by anti-SARS-CoV-2 spike antibody levels; and cell immunogenicity, as measured by an increase in SARS-CoV-2 cytotoxic cellular response in vitro. The secondary outcome was the effect of the mRNA vaccines on glycemic control in patients with T1D, as measured by continuous glucose monitoring (CGM) (3). Samples and data were analyzed before vaccination and after doses 1 and 2.

Immunological Studies

SARS-CoV-2 Spike Antibody Detection

The humoral response was analyzed using Elecsys Anti-SARS-CoV-2 serology test (Roche Diagnostics, Basel, Switzerland), which captured IgG, IgM, and, to a lesser extent, IgA against SARS-CoV-2 spike antigen (receptor-binding domain), with signal-to-cutoff values of $\geq$1.0 reported as positive (14). An in vitro neutralization assay was used as previously described (15) to validate anti-SARS-CoV-2 antibody titers detected in seronegative vaccinated patients with T1D by performing a Spearman correlation analysis between antibody titers detected by the neutralization and Elecsys assays.

In Vitro Immune Cellular Response

Peripheral blood mononuclear cells (PBMCs) (1×10^6) (16) obtained from frail subjects or patients with T1D before and after vaccination were cultured with and without SARS-CoV-2 spike and nucleocapsid recombinant proteins (PR-nCoV-3/PR-nCoV-1 500 ng/mL; Novatein Biosciences, Inc., Woburn, MA) for 48 h (17). Vaxigrip (quadrivalent split-virion influenza vaccine peptides 0.25 μg/mL; Sanofi-Pasteur) and glutamate transporter-1 50 μg/mL (GenScript, Piscataway, NJ) were included as positive and negative controls. Supernatants were tested for perforin/granzyme A (HCD8MAG-15K; Merck Millipore, Burlington, MA) and T-cell–related cytokines (M500KCAF0Y; Bio-Rad Laboratories, Hercules, CA) by a Bio-Plex 200 system. An increase in cytotoxic response was assessed as a fold increase $>$0.1 for perforin and $>$0.01 for granzyme A, respectively. Cut points of 0.1 and 0.01 were defined on the basis of the difference detected for each analyte, measured at each time point, and normalized to the baseline value. To test the specific response to SARS-CoV-2 antigens, the number of interferon-γ (IFN-γ)–producing cells (BD Biosciences, Franklin Lakes, NJ) was assessed by ELISpot assay as previously described (17).

Statistical Analysis

Fisher exact test, one-way and two-way ANOVA, Kruskal-Wallis test adjusted for multiple comparisons, and Mann-Whitney *U* test were used in the analyses of baseline characteristics, side effects, humoral and cellular response, and CGM parameters. Multivariable logistic regression was used to model the relationships between cofactors and cellular response (Stata 12 software; StataCorp). Statistical significance was determined at $\alpha < 0.05$. GraphPad Prism 7 (GraphPad Software, San Diego, CA) was used to generate graphs.

Data and Resource Availability

The data sets and resources generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

RESULTS

Patient Characteristics

We included 375 patients consecutively administered a SARS-CoV-2 mRNA vaccine, of whom 326 had long-term T1D (22.9 ± 14.2 years) and 49 had no diabetes but were considered to be medically frail or were caregivers/family members of patients with T1D (Supplementary Fig. 1 and Table 1). The mean age of patients with T1D was 45.9 ±

Table 1—Baseline characteristics of patients included in the study

	Patients With T1D (n = 326)	Subjects Without Diabetes° (n = 49)	P
Age, mean ± SD, years	45.9 ± 9.0	61.0 ± 12.9	<0.0001
Male sex, n (%)	180 (54.9)	21 (42.9)	0.12
Diabetes duration, mean ± SD, years	22.9 ± 14.2	—	
BMI, mean ± SD, kg/m^2	25.1 ± 4.1	26.4 ± 4.9	0.16
Comorbidities, n (%)			
Hypertension	85 (25.9)	18 (36.7)	0.13
Cardiovascular disease	18 (5.5)	1 (2.0)	0.48
Cerebrovascular disease	12 (3.7)	2 (4.1)	0.70
Chronic kidney disease†	14 (4.3)	1 (2.0)	0.70
Diabetic neuropathy	32 (9.8)	—	
Diabetic retinopathy	86 (28.3)	—	
Malignancy	9 (2.9)	0	0.61
Autoimmune diseases, n (%)			
Autoimmune thyroiditis	72 (23.5)	6 (12.2)	<0.0001
Other autoimmune disease	24 (7.8)	5 (10.2)	0.57
Diabetes treatment, n (%)			
Insulin	326 (100)	—	
Other treatments			
ACE inhibitors	39 (11.9)	10 (20.4)	0.11
Angiotensin II receptor blockers	31 (9.5)	5 (10.2)	0.80
β-Blockers	32 (9.8)	4 (8.2)	0.99
Aspirin	45 (13.8)	8 (16.3)	0.66
Statins	27 (12)	4 (14)	0.75

°Subjects without diabetes include frail patients without diabetes as defined on the basis of the guidelines issued by the Italian Ministry of Health (i.e., elderly subjects >75 years old or of any age with a respiratory illness, severe cardiovascular disease, neurological disabilities, multiple sclerosis, cystic fibrosis, kidney failure, autoimmune diseases, liver disease, stroke and cerebrovascular disease, cancer, Down syndrome, organ or bone marrow transplant, severe obesity) and caregivers/family members of patients with T1D. †Chronic kidney disease defined as estimated glomerular filtration rate ≤60 mL/min/m^2.

9.0 years, and 180 (55%) were male. The mean age of subjects without diabetes was 61.0 ± 12.9 years, and 21 (43%) were male (Table 1). No differences were observed with regard to type of vaccine administered (Supplementary Table 1), BMI, concomitant therapy (except for insulin treatment), and major clinical comorbidities, with a higher frequency of autoimmune thyroiditis observed in patients with T1D (Table 1).

Safety

No differences were observed between patients with T1D and subjects without diabetes with regard to local and systemic side effects after vaccination (Supplementary Fig. 2A and *B*). The most common side effect was local pain reported equally after dose 1 and 2 of the vaccine (72.6% vs. 73.7%, P = 0.78) (Supplementary Fig. 2A and *B*). Systemic adverse events, consisting mainly of weakness and fever, were more frequent after dose 2 (Supplementary Fig. 2A and *B*).

Immunogenicity

Humoral Immunity

With regard to SARS-CoV-2 humoral response, patients with T1D who were seronegative for COVID-19 showed an increase in median IgG levels after both dose 1 and dose 2 (60.4 and 2058.0 units/mL, respectively) (Fig. 1*A–C*). This observation was paralleled in subjects without diabetes at both time points (46.3 and 1,965.0 units/mL, respectively) (Fig. 1*A–C*), with a response rate comparable between the two groups. These data indicate that the administration of two doses of the SARS-CoV-2 mRNA vaccine elicited a humoral response in patients with T1D. In a subgroup analysis performed on 15% (49 of 326) of patients with T1D and 14.3% (7 of 49, P = 0.99) of subjects without diabetes who underwent full vaccination but were seropositive for COVID-19 (i.e., experienced asymptomatic SARS-CoV-2 infection, baseline signal-to-cutoff IgG value of ≥1.0), the analysis of the humoral response revealed no differences between the two groups (Supplementary Fig. 3). Finally, our assay captured neutralizing activity as shown by a positive correlation between anti-SARS-CoV-2 titers determined by our assay with titers of neutralizing antibodies as measured by an in vitro neutralization assay (Fig. 1*D*).

Cellular Immunity

To address whether an immune cytotoxic response against SARS-CoV-2 was elicited with vaccination, we rechallenged isolated PBMCs with SARS-CoV-2 peptides at baseline and

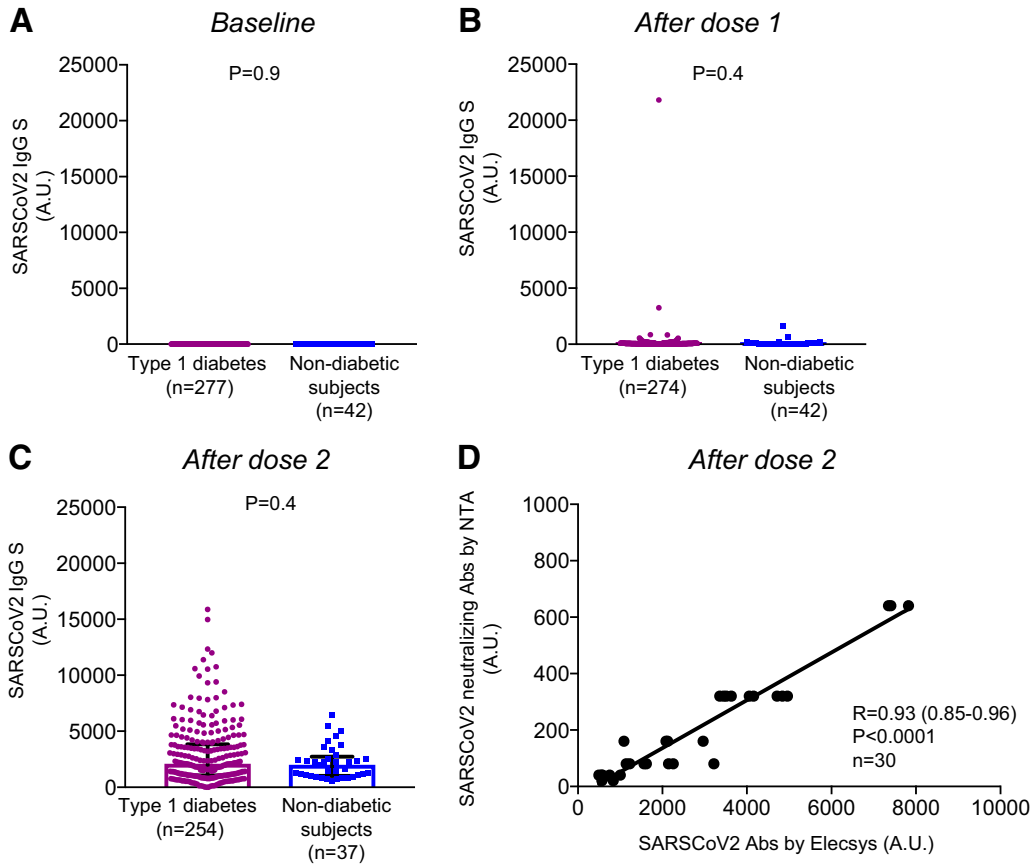

Figure 1—Anti-SARS-CoV-2 antibody response in patients with T1D and subjects without diabetes. *A*–*C*: Box plots representing anti-SARS-CoV-2 spike (S) antibody levels measured in patients with T1D and subjects without diabetes at baseline (*A*), after the first dose (*B*), and after the second dose (*C*) of the SARS-CoV-2 mRNA vaccines. Anti-SARS-CoV-2 antibody titers are reported as median with interquartile range. *D*: Line graph showing the correlation between SARS-CoV-2 antibody titers detected by an in vitro neutralization assay and through the Elecsys assay ($n = 30$). Measurements for after dose 1 were performed 3–4 weeks after the first dose, and measurements after dose 2 were performed 4 weeks after the second dose. Abs, antibodies; A.U., arbitrary unit; NTA, neutralization assay.

after doses 1 and 2 in a MILLIPLEX MAP Human assay. Patients with T1D showed no increase in granzyme A and perforin SARS-CoV-2–specific T-cell release in the supernatant after vaccination compared with baseline, while a 2–3-fold increase in both granzyme A and perforin production was evident in subjects without diabetes (Fig. 2*A* and *B*), which was also confirmed by testing negative (<1-fold increase) and positive (10- and 7-fold increase for granzyme A and perforin, respectively) controls. Interestingly, only 30% of patients with T1D showed an increased SARS-CoV-2–specific T-cell cytotoxic response after dose 1 compared with 80% of subjects without diabetes (Fig. 2*C*). This observation was confirmed after dose 2 in patients with T1D, with 22% developing/maintaining an increased SARS-CoV-2–specific T-cell cytotoxic response, although the rate of subjects without diabetes developing a cytotoxic response was lower (57%) (Fig. 2*D*). Furthermore, the reduced cytotoxic response detected in T1D was confirmed after controlling for other factors potentially involved (age, sex, and concomitant diseases) (Supplementary Table 2). These findings suggest that SARS-CoV-2 mRNA vaccines fail to elicit a robust cytotoxic response against SARS-CoV-2 in the majority of patients with T1D. Finally, a multiplex T-cell–related cytokine analysis revealed lower levels of interleukin-2 and tumor necrosis factor-α measured in the supernatant of PBMCs cultured with SARS-CoV-2 peptides in patients with T1D compared with subjects without diabetes after vaccination (Fig. 3*A*), which was associated with a low response in an IFN-γ ELISpot assay (Fig. 3*B*), regardless of the type of mRNA vaccination administered, thus confirming the existence of an altered immune cellular response to SARS-CoV-2 mRNA two-dose vaccination in T1D.

Glycemic Control

Given that COVID-19 is associated with the development of dysglycemia and diabetes, we finally assessed whether the administration of SARS-CoV-2 mRNA vaccine may affect glycometabolic control in patients with T1D. Data collected using CGM showed no difference in all the parameters examined at each time point (Supplementary Table 3). Moreover, a multivariable analysis showed no association between estimated HbA_{1c} levels and cytotoxic

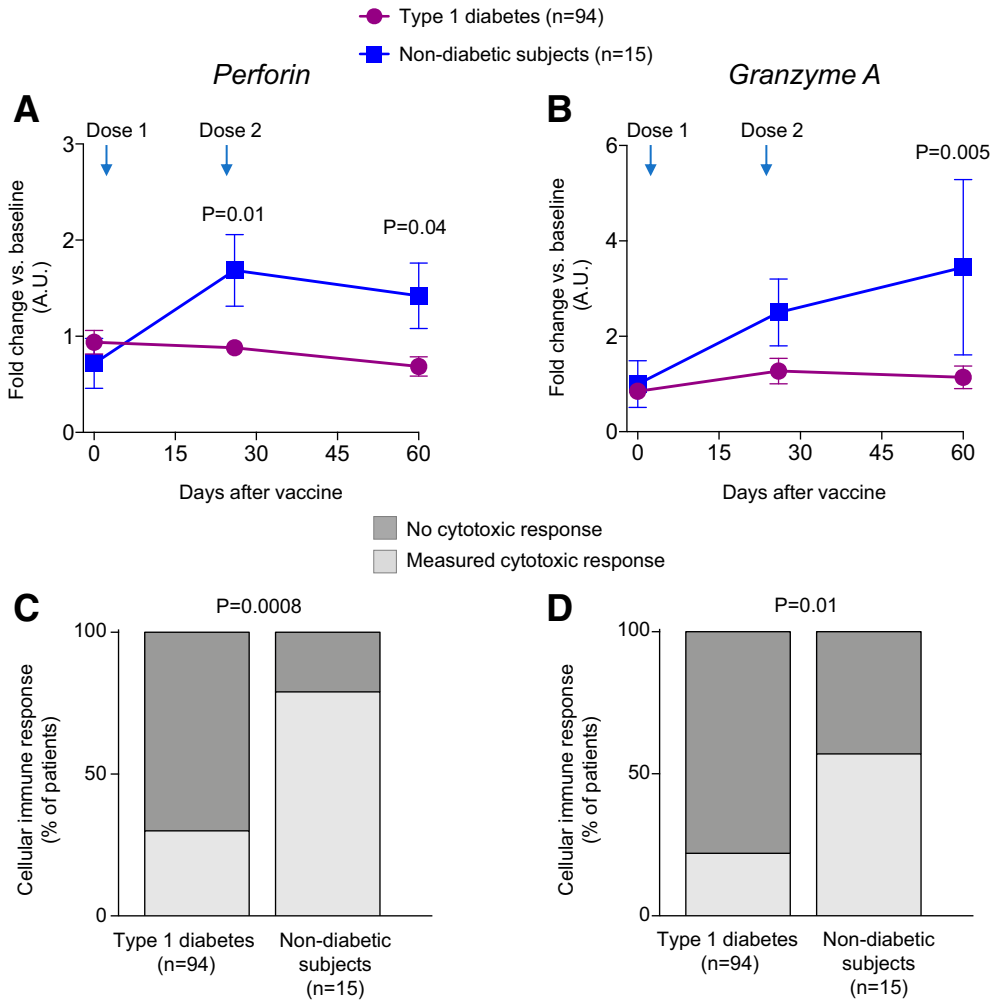

Figure 2— Cytotoxic response to the SARS-CoV-2 peptides after prime and boost doses of SARS-Cov-2 mRNA vaccines administered to patients with T1D and subjects without diabetes. *A* and *B*: Line graphs representing normalized secretion of SARS-CoV-2–specific T-cell cytotoxic factors perforin (*A*) and granzyme A (*B*), as measured in the supernatant of PBMCs obtained from patients with T1D or subjects without diabetes at each time point (baseline, after dose 1, and after dose 2) and cultured in the presence or absence of SARS-CoV-2 peptides for 48 h. Data are mean ± SEM. Secretion data have been normalized to baseline levels for each cytokine analyzed. Cut points of 0.1 and 0.01 were assessed on the basis of the difference observed in the levels of each analyte (perforin and granzyme A, respectively) as measured at each time point compared with baseline and normalized to the baseline value. Analysis was performed for after dose 1 at 3–4 weeks after the first dose and for after dose 2 at 4 weeks after the second dose. *C*: Bar graph of the percentage of patients with T1D compared with subjects without diabetes showing increased or no change in the SARS-CoV-2–specific T-cell cytotoxic response before receiving the second dose of SARS-Cov-2 mRNA vaccines. *D*: Bar graph of the percentage of patients with T1D compared with subjects without diabetes showing increased or no change in the SARS-CoV-2–specific T-cell cytotoxic response at 4 weeks of follow-up after administration of the second dose of SARS-Cov-2 mRNA vaccines. The SARS-CoV-2–specific T-cell cytotoxic response was analyzed as an increase or lack of increase observed in both perforin and granzyme A levels at each time point. A.U., arbitrary unit.

response to vaccination in patients with T1D after adjusting for age, sex, and concomitant therapies (P = 0.23 and P = 0.65 for response to doses 1 and 2, respectively). These findings suggest that the administration of the SARS-CoV-2 mRNA vaccine is not associated with altered glycometabolic control in patients with T1D.

DISCUSSION

Our study evaluated the safety, immunogenicity, and glycometabolic effects of two doses of SARS-CoV-2 mRNA vaccines in patients with T1D. No differences were observed with regard to the humoral response or the incidence of side effects in patients with T1D compared with subjects without diabetes, and no effects on glycometabolic control were observed using CGM analysis during follow-up. Interestingly, in the majority of patients with T1D, both dose 1 and dose 2 of SARS-CoV-2 mRNA vaccines were not associated with an increase in cytotoxic factors granzyme A and perforin or with an increase in the production of the T-cell–related cytokines interleukin-2 and tumor necrosis factor-α compared with subjects without diabetes, who showed an

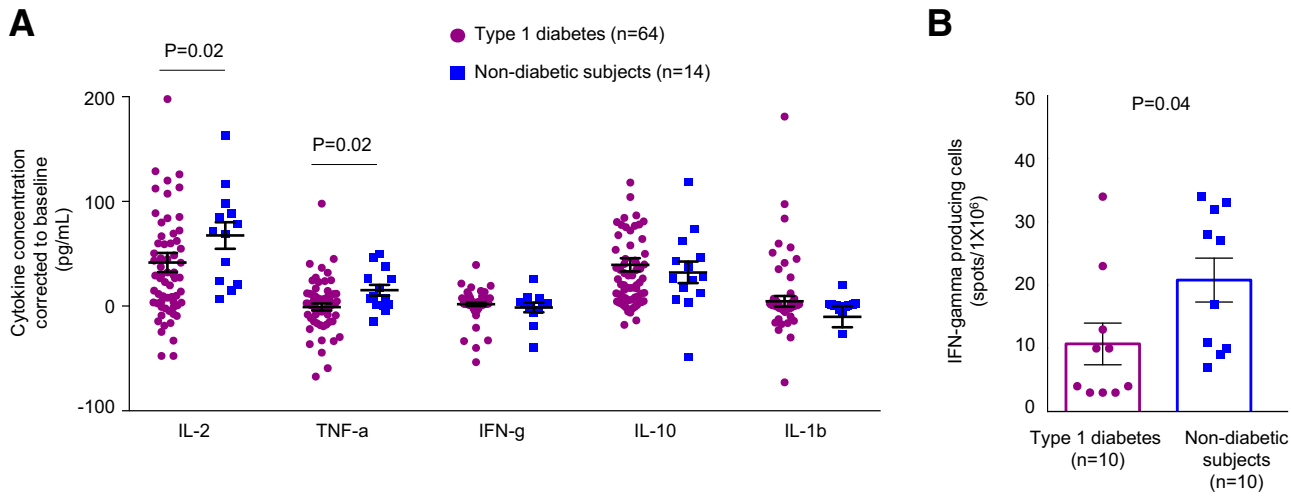

Figure 3—T-cell–related cytokines and immune response to SARS-CoV-2 peptides after administration of SARS-Cov-2 mRNA vaccines in patients with T1D and subjects without diabetes. *A*: Dot plots representing secretion of SARS-CoV-2–specific T-cell–related cytokines as measured in the supernatant of PBMCs obtained from patients with T1D or from subjects without diabetes at baseline and after dose 2 and cultured in the presence or absence of SARS-CoV-2 peptides for 48 h. Data are mean ± SEM of secretion levels corrected to baseline levels for each cytokine analyzed. *B*: Bar graphs representing the number of IFN-γ (IFN-g) spots detected by ELISpot analysis using PBMCs isolated from patients with T1D (n = 10) and subjects without diabetes (n = 10) after the administration of the SARS-CoV-2 mRNA vaccines and following challenge with spike and nucleocapsid SARS-CoV-2 peptides. Data are mean ± SEM. IL, interleukin; TNF-a, tumor necrosis factor-α.

increased rate of both cytotoxic factors and cytokines after vaccination. The SARS-CoV-2 mRNA vaccines have been shown to elicit a humoral and T-cell–specific immune response in healthy subjects (18,19), but little is known about their effects in patients with T1D. An impairment in the immune response following vaccination in patients with T1D has been previously hypothesized for other immunization strategies, such as influenza, rotavirus, and *Haemophilus influenzae* type B (6,8), and attributed to an impaired cellular immune response. Therefore, boosting immunization strategies with multiple doses has been recommended (8,20). Indeed, immune dysregulation of both T- and B-cell compartments is a key feature of patients with T1D from the onset of the disease and may indicate abnormalities in the immune response (21,22), including a higher risk of developing infectious disease (23,24). This was particularly evident during the COVID-19 pandemic, with patients with T1D experiencing severe COVID-19 disease and worsened outcomes compared with the general population without diabetes (1,2,11). In our study, patients with T1D did not show an increase in T-cell–specific SARS-CoV-2 cytotoxic factor release (granzyme A and perforin), which may indicate a defective ability in inactivating the virus. Indeed, perforin and granzyme A levels, as observed for other vaccines and immunization strategies (25,26), detected after vaccination increased in subjects without diabetes in response to SARS-CoV-2 in vitro challenge, while no effect was observed in the majority of patients with T1D. This suggests a reduced cytotoxic effector function in T1D and a less immunogenic/efficient vaccination in these patients. Nevertheless, no significant differences were observed in SARS-CoV-2 spike–specific neutralizing antibody titers between patients with T1D and subjects without diabetes. To our knowledge, this study is the first to demonstrate the safety and immunogenicity of SARS-CoV-2 mRNA vaccines in a large cohort of patients with T1D without any significant perturbation in CGM parameters (13,27).

We acknowledge that this study has some limitations. The study design may have led to potential selection bias primarily due to the COVID-19 pandemic, such as the smaller and not fully age-matched frail control population and the limited number of samples available for some analyses (e.g., ELISpot), and the assay used captured only one aspect of the vaccine-specific cellular response.

In summary, an impaired cytotoxic SARS-CoV-2–specific cellular immune response has been observed in the majority of patients with T1D following two doses of SARS-CoV-2 mRNA vaccines, with the humoral response and glycemic control unaffected.

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and G.R. performed experiments and analyzed data. I.P., L.M., P.S.M., L.P., A.R., E.C., A.M.B., E.L., C.M., and M.M. collected human data and samples. S.A., S.R., M.Gallie., C.B., F.F., M.Galli, M.R.G., and G.V.Z. coordinated and designed the research and edited the manuscript. P.F. conceived the idea, designed the study, and wrote and edited the manuscript. P.F. 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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