Diabetes Affects Antibody Response to SARS-CoV-2 Vaccination in Older Residents of Long-term Care Facilities: Data From the GeroCovid Vax Study

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OBJECTIVE

Type 2 diabetes may affect the humoral immune response after vaccination, but data concerning coronavirus disease 19 (COVID-19) vaccines are scarce. We evaluated the impact of diabetes on antibody response to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination in older residents of long-term care facilities (LTCFs) and tested for differences according to antidiabetic treatment.

RESEARCH DESIGN AND METHODS

For this analysis, 555 older residents of LTCFs participating in the GeroCovid Vax study were included. SARS-CoV-2 trimeric S immunoglobulin G (anti-S IgG) concentrations using chemiluminescent assays were tested before the first dose and after 2 and 6 months. The impact of diabetes on anti-S IgG levels was evaluated using linear mixed models, which included the interaction between time and presence of diabetes. A second model also considered diabetes treatment: no insulin therapy (including dietary only or use of oral antidiabetic agents) and insulin therapy (alone or in combination with oral antidiabetic agents).

RESULTS

The mean age of the sample was 82.1 years, 68.1% were women, and 25.2% had diabetes. In linear mixed models, presence of diabetes was associated with lower anti-S IgG levels at 2 ($\beta = -0.20$; 95% CI −0.34, −0.06) and 6 months ($\beta = -0.22$; 95% CI −0.37, −0.07) after the first vaccine dose. Compared with those without diabetes, residents with diabetes not using insulin had lower IgG levels at 2- and 6-month assessments ($\beta = -0.24$; 95% CI −0.43, −0.05 and $\beta = -0.30$; 95% CI −0.50, −0.10, respectively), whereas no differences were observed for those using insulin.

CONCLUSIONS

Older residents of LTCFs with diabetes tended to have weaker antibody response to COVID-19 vaccination. Insulin treatment might buffer this effect and establish humoral immunity similar to that in individuals without diabetes.

Older adults residing in long-term care facilities (LTCFs) have been negatively affected by the coronavirus disease 2019 (COVID-19) pandemic, with an infection

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rate of 45% and a mortality rate of 23% during the first pandemic waves, when no vaccine was available (1). Indeed, these settings involve vulnerable individuals, in terms of advanced age and comorbidities, along with environmental characteristics that per se facilitate the spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (2). Vaccination against COVID-19 has proven to be a safe and effective measure for reducing the mortality and morbidity of the disease in the general population (3–5). However, older and frail individuals (especially LTCF residents) were not included in the first large SARS-CoV-2 vaccine trials. Therefore, the need to assess the immunogenicity and effectiveness of the vaccination against SARS-CoV-2 in this vulnerable population, as well as to identify factors potentially influencing vaccine response, remains fundamental (3).

Type 2 diabetes has been recognized as a risk factor for severe COVID-19 outcomes, especially intensive care unit admission and mortality (4,5). In a large meta-analysis (N = 16,003), presence of diabetes in patients with COVID-19 was associated with a twofold increased risk of severe COVID-19 disease and related mortality (6). Although attenuated, this detrimental effect was also confirmed after taking into account advanced age or other conditions associated with both diabetes and COVID-19 severity, such as obesity (7,8). Among the mechanisms underlying this greater vulnerability, poor glycemic control may impair the immune system of patients with diabetes, exposing them to higher risk and severity of infectious diseases (9–11). Older patients with diabetes are considered a high-risk population for infectious diseases, including COVID-19 infection. Vaccination against common pathogens (e.g., influenza, pneumococcal infection, and hepatitis B) is strongly recommended in this population (12,13). Therefore, one may hypothesize that the detrimental effect of diabetes on immune function may also blunt the response to vaccination. Some studies have evaluated the impact of diabetes on response to influenza, hepatitis B, pneumococcal disease, and varicella-zoster vaccination, with inconsistent findings (14,15). Currently, there are limited data regarding the immune response to vaccines against COVID-19 in older individuals with diabetes (16–19) and whether antidiabetic treatments (9,20–23) may have an impact on immune system response. Indeed, insulin influences not only innate but also acquired immunity by preserving T cells from diabetes-induced apoptosis (9,22). Therefore, we aimed to assess whether the humoral immune response to the SARS-CoV-2 vaccine differed between older residents of LTCFs with and without diabetes and explore possible modifying effects according to antidiabetic treatment regimens. To test our hypothesis, we used longitudinal data from the GeroCovid Vax study in older adults living in LTCFs throughout Italy.

RESEARCH DESIGN AND METHODS

Study Population

This study used data from GeroCovid Vax, a multicenter study promoted by the Italian Society of Gerontology and Geriatrics (Florence, Italy) and the Istituto Superiore di Sanità (Rome, Italy) and sponsored by the Agenzia Italiana del Farmaco. GeroCovid Vax is a prospective study that aims at assessing the efficacy and safety of SARS-CoV-2 vaccination in older residents of Italian LTCFs. Details on the study protocol have been previously published (2,24). Briefly, the study included residents of LTCFs who had received at least one dose of the anti–SARS-CoV-2 vaccine, were aged $\geq$60 years, and had an estimated life expectancy and expected stay in the LTCF $\geq$3 months. Data collection started in January 2021, and for each individual, the observation period lasted 12 months, with assessments after 7 days from vaccine dose administration and at 2, 6, and 12 months after the first dose. For all 3,268 enrolled participants, we recorded all potential vaccine adverse effects, new cases of COVID-19, emergency department visits, unplanned hospitalizations, and mortality after vaccination. In a representative subsample of 611 residents, we also monitored humoral immune response before and after the first vaccine dose.

In the current study, we used all available data from this subsample until 6 months from the first vaccine dose. Because our sample included residents who received the first vaccine dose from January to June 2021, the observation period ended in December 2021. We did not consider the 12-month follow-up, because some of our sample received a booster dose after the 6-month assessment, and further stratification of our sample would have jeopardized the statistical significance of the analyses. From the initial sample of 611 participants, we excluded 56 individuals who had incomplete health data concerning chronic diseases and drugs used, obtaining a final analytic sample of 555 individuals. Supplementary Table 1 underlines clinical differences between participants included versus excluded from the current study. We found that those included were slightly younger, had worse mobility levels, and were more likely to have previously had COVID-19 infection. They also showed a higher prevalence of diabetes, chronic kidney disease, and cognitive disorders but a lower frequency of cancer, peripheral artery disease, and depressive disorders. Overall, the total numbers of chronic diseases (excluding diabetes) and drugs used were lower in included than excluded participants.

The study was approved by the Ethical Committee at the Spallanzani Institute (permission no. 264/2021; 26 January 2021; Rome, Italy) and the local ethics committees at the participating sites.

Data Collection

Before beginning the study, physicians and researchers skilled in the geriatric field at the participating sites were trained for data collection and recording into an e-registry developed by Bluecompanion Ltd. (London, U.K.). The following information was obtained for all participants: sociodemographic data (age, sex, and ethnicity), mobility level (categorized as walking independently or with walking aids, moving with a wheelchair, or bedridden), chronic diseases, and drugs used. Moreover, for those with available data, we assessed frailty, according to Pedone et al. (25), as the presence of at least two of the following anamnestic criteria: unintentional weight loss ($>$4.5 kg in the last year), exhaustion (i.e., feeling of needing an effort to do everything for $>$3 to 4 days in the previous week), and reduced physical activity (having performed $<$2 to 4 h of light exercise weekly).

The primary exposure of this study was the presence of type 2 diabetes, derived both from participants' medical history and the list of drugs used. Information regarding all drug treatments

was obtained, and particularly for the purpose of the study, we categorized antidiabetic treatments as follows: no insulin therapy (including dietary control only or use of oral antidiabetic agents) or insulin therapy (insulin alone or in combination with oral antidiabetic agents).

Chronic conditions (except for diabetes) included the following: osteoarthritis, osteoporosis, hypertension, atrial fibrillation, ischemic, arrhythmic or valvular heart diseases, heart failure, peripheral artery diseases, chronic respiratory diseases, obesity, depressive disorders, Parkinson's disease or parkinsonism, thyroid disorders, epilepsy, anxiety, hyperuricemia/gout, urologic disorders, gynecologic conditions, dermatologic diseases, chronic liver diseases, biliary disorders, eye/ear/nose/throat disorders, previous stroke, chronic kidney failure, cancer, immune system disorder, and inflammatory bowel diseases. Presence of cardiovascular diseases (CVDs) was defined as the presence of atrial fibrillation, ischemic, arrhythmic or valvular heart diseases, or heart failure. Information on cognitive disorders (including cognitive impairment or dementia) and on the drugs chronically used by the participants was also collected from anamnestic data and medical records at the participants' LTCFs. Finally, baseline prevalence of poor nutritional status was evaluated by the study physicians based on a clinical evaluation of the resident, considering anthropometric and clinical parameters.

COVID-19–Related Information

History of SARS-CoV-2 infection (determined by real-time PCR testing) was retrieved for each participant as well as the date, type, and number of administered doses of SARS-CoV-2 vaccine. The campaign for COVID-19 vaccination in LTCFs in Italy started at the end of December 2020, and mRNA vaccines were mainly used (Moderna mRNA-1273 or Cominarty BNT162b2). National recommendations indicated administering only one vaccine dose in residents with SARS-CoV-2 infection in the previous 6 months; otherwise, a two-dose vaccination cycle was indicated (26).

Humoral Immune Response

Serum levels of SARS-CoV-2 trimeric S immunoglobulin G (anti-S IgG) were evaluated before vaccination (T0) and after 2 (T1) and 6 months (T2) from the first dose. Blood samples were collected at the LTCFs in the morning after an overnight fast and then prepared and stored according to standardized procedures. In particular, serum samples were collected in Serum Separator Tubes (BD Diagnostic Systems, Franklin Lakes, NJ) and centrifuged at room temperature at 1,600 rpm for 10 min. Aliquots were transferred to 2 mL polypropylene in screw-cap cryotubes (Nunc; Thermo Fisher Scientific, Waltham, MA) and immediately frozen at -20°C. Frozen sera were sent to the Istituto Superiore di Sanità laboratory and stored at -80°C. Antibody levels were assessed by the LIAISON SARS-CoV-2 TrimericS IgG chemiluminescent assay (DiaSorin, Saluggia, Italy), using the trimeric S antigen stabilized in its native form. The LIAISON XL fully automated chemiluminescence analyzer automatically derives SARS-CoV-2 anti-S IgG antibody concentrations expressed as binding antibody units (BAU/mL; upper measurable limit 2,080 BAU/mL). According to the manufacturer's instructions, antibody levels $\geq$33.8 BAU/mL were considered positive. In case of antibody levels overcoming the upper limit of the assay, samples were diluted at a 1:20 ratio and reanalyzed.

Statistical Analysis

Baseline characteristics of participants by presence of diabetes and antidiabetic treatment are described as mean (SD) for continuous variables and as absolute and relative frequencies for categorical variables. Participants with and without diabetes were compared using the Student *t* test and χ^2 test, as appropriate. Comparison between participants with diabetes under different treatments was made through ANOVA, Kruskal-Wallis test, or χ^2 test.

Distribution of anti–SARS-CoV-2 IgG levels at T0, T1, and T2 in participants with and without diabetes (considering the sample as a whole and stratified by COVID-19 history) is expressed as geometric mean (SD) and illustrated through box plots. Comparison between participants with and without diabetes at each assessment was performed using the Wilcoxon test. The association between presence of diabetes and antibody response over time was studied through linear mixed models. These models included a random intercept in which the effects were nested within the study site and individuals (to take into account possible differences in diabetes management between participating centers [27]), and the interaction diabetes * time. Strength of the association between diabetes and antibody response is expressed as β coefficient and 95% CI. The β coefficient for the interaction term estimates the extent to which the difference in antibody levels between individuals with and without diabetes changes at T1 or T2 with respect to T0. Considering the nonnormal distribution of antibody levels in the population, we performed a log transformation. Models were adjusted for potential confounders, including, first, age, sex, race, previous COVID-19 infection, and the number of vaccine doses received, and second, also, the type of COVID-19 vaccine, mobility level, cognitive disorders, and the number of chronic diseases. A third model was run after adjusting for age, sex, race, previous COVID-19 infection, number of vaccine doses received, type of COVID-19 vaccine, mobility level, cognitive disorders, and other single chronic conditions that could affect immune response (e.g., use of corticosteroids, CVDs, osteoarticular diseases, chronic respiratory diseases, immune system disorders, chronic kidney disease, and poor nutritional status). Similar models were performed to evaluate the association of type 2 diabetes and ongoing antidiabetic treatment with antibody response. Antidiabetic treatment was categorized as follows: not using insulin therapy or using insulin treatment (insulin alone or in combination with antidiabetic oral agents). As a sensitivity analysis, first we excluded those who received the Moderna mRNA-1273 vaccine, because previous work showed higher immunogenicity for that vaccine in older people, and its frequency differed among the groups with and without diabetes in our sample (28). Second, we performed analyses only among participants who were nonfrail (n = 241) to minimize the possible confounding effect of frailty in our results. Third, considering the well-known sex-related differences in immune response to infections and vaccines (29), we ran stratified analyses to test the studied association in men and women. All analyses were performed using R statistical software (30).

Table 1—Characteristics of total sample and by presence of diabetes

	All (N = 555)	No diabetes (n = 415)	Diabetes (n = 140)	P
Age (years)	82.1 (9.6)	82.6 (9.8)	80.7 (8.7)	0.037
Sex (female)	378 (68.1)	286 (68.9)	92 (65.7)	0.55
Mobility level				0.033
Independent/walks with aids	308 (55.5)	235 (56.6)	73 (52.1)	
Moves with wheelchair	166 (29.9)	112 (27.0)	54 (38.6)	
Bedridden	53 (9.5)	44 (10.6)	9 (6.4)	
Vaccine type				0.001
Cominarty BNT162b2	471 (84.9)	338 (81.4)	133 (95.0)	
Moderna mRNA-1273	76 (13.7)	70 (16.9)	6 (4.3)	
Second vaccine dose received	319 (58.3)	234 (57.4)	85 (61.2)	0.493
Previous COVID-19	226 (40.8)	183 (44.2)	43 (30.7)	0.007
Chronic kidney disease	73 (13.2)	49 (11.8)	24 (17.1)	0.125
Cancer	43 (7.8)	34 (8.3)	9 (6.4)	0.598
Osteoarticular diseases	279 (50.3)	206 (49.6)	73 (52.1)	0.678
Hypertension	402 (72.4)	290 (69.9)	112 (80.0)	0.027
CVDs	293 (52.8)	204 (49.2)	89 (63.6)	0.004
Peripheral artery diseases	74 (13.3)	45 (10.8)	29 (20.7)	0.005
Chronic respiratory diseases	115 (20.7)	83 (20.0)	32 (22.9)	0.548
Obesity	52 (9.4)	32 (7.7)	20 (14.3)	0.032
Poor nutritional status	76 (13.7)	58 (14.0)	18 (12.9)	0.397
Depressive disorders	258 (46.5)	191 (46.0)	67 (47.9)	0.781
Cognitive disorders	385 (69.4)	304 (73.3)	81 (57.9)	0.001
Parkinson's disease	48 (8.6)	39 (9.4)	9 (6.4)	0.364
Anxiety	114 (20.5)	90 (21.7)	24 (17.1)	0.303
Total n of chronic diseases	4.7 (2.3)	4.6 (2.2)	5.0 (2.5)	0.034
Total n of drugs/day	5.0 (3.4)	4.8 (3.1)	5.6 (4.2)	0.021

Data are given as n (%); n = 28 participants had missing information on mobility level, n = 5 on malnutrition and chronic kidney disease, and n = 8 on type of vaccination.

RESULTS

Table 1 shows the characteristics of the total sample according to diabetes status. The mean age of participants was 82.1 years, 68.1% were women, and 97.3% were Caucasian. Almost half of the participants in the entire study group moved with a wheelchair or were bedridden, and 69.4% had cognitive disorders. Concerning COVID-19 vaccination, 84.9% received Cominarty BNT162b2, and 58.3% had been administered two vaccine doses. The mean number of chronic diseases and daily drugs was 4.7 (SD 2.3) and 5.0 (SD 3.4), respectively, in the whole population. In addition to cognitive disorders, the most common chronic conditions were hypertension (72.4%), CVDs (52.8%), and osteoarticular diseases (50.3%). A total of 140 (25.2%) of the 555 included participants were affected by diabetes. Compared with participants without diabetes, we found that those with diabetes were more likely to have received the Cominarty BNT162b2 vaccine, be younger, be less independent in mobility, and have arterial hypertension, CVDs, and artery diseases, as well as obesity. Moreover, participants with diabetes had a lower prevalence of previous COVID-19 infection and cognitive disorders. Of the 140 participants with diabetes, 111 had available information on ongoing treatments: 37 (33.3%) were not receiving any pharmacologic treatment (diet only), 34 (30.6%) were taking antidiabetic oral agents, and 40 (36%) were receiving insulin (alone or in combination with antidiabetic oral agents). We compared clinical characteristics according to antidiabetic treatments (Supplementary Table 2). We found that residents using insulin had a significantly higher prevalence of chronic kidney disease and, along with those not receiving pharmacologic treatments, showed higher frequencies of hypertension and peripheral artery diseases.

Figure 1 presents the distribution of antibody levels in residents with and without diabetes over the observation period. We found that participants with diabetes had lower anti-S IgG after 2 and 6 months from the first vaccine dose compared with those without diabetes. This trend was slightly more marked among those with a history of SARS-CoV-2 infection (Supplementary Fig. 1 and Table 3). In order to take into account the impact of potential confounders (including previous infection), we tested for differences according to presence of diabetes using linear mixed regression models (Table 2). We found that residents with diabetes had lower antibody levels than those without, both at T1 (β = −0.20; 95% CI −0.34, −0.06) and T2 follow-up assessments (β = −0.22; 95% CI −0.37, −0.07; Table 2). Regarding antidiabetic treatments, we found reduced IgG levels for those not undergoing insulin therapy (diet alone and antidiabetic oral agent use), both at T1 (β = −0.24, 95% CI −0.43, −0.05) and T2 (β = −0.30, 95% CI −0.50, −0.10) compared with individuals without diabetes; no significant differences were observed for those receiving insulin treatment compared with those without diabetes. No substantial variations in the estimated coefficients emerged when adjusting the model for single chronic conditions and drugs that could affect vaccine response (Supplementary Table 4). Similar results were observed after excluding those who received the Moderna mRNA-1273 vaccine (data not shown) and when considering only nonfrail individuals (Supplementary Table 5). Concerning possible sex-specific differences, we found that the association between diabetes and antibody levels was confirmed among women but not among men, likely because of the small number of men included in the study and the limited statistical power (Supplementary Table 6).

CONCLUSIONS

The immune response of older adults with diabetes to SARS-CoV-2 vaccination remains to be elucidated. This study

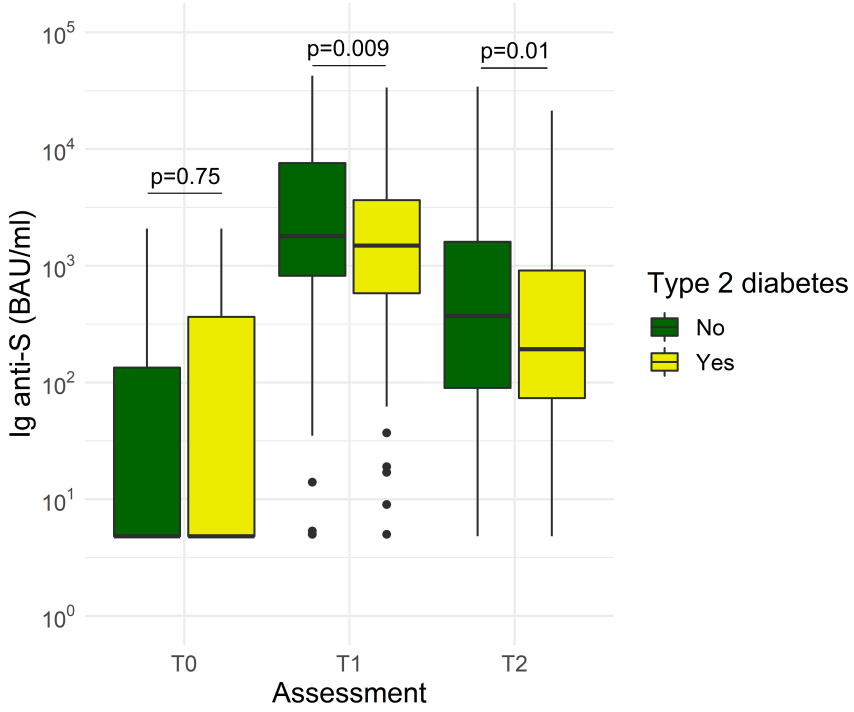

Figure 1—Log10-transformed anti-S antibody levels in participants with and without diabetes before the vaccination (T0) and after 2 (T1) and 6 months (T2). *P* values refer to the comparison by Wilcoxon test between diabetes and no diabetes at each assessment.

found that SARS-CoV-2 vaccination was associated with reduced humoral immune response in older residents of LTCFs with type 2 diabetes compared with older residents without diabetes 2 and 6 months after the first vaccine dose. Interestingly, the diabetes-related disadvantage in vaccine antibody response was not observed in individuals with diabetes undergoing insulin therapy, who had similar antibody kinetics to those without diabetes.

The focus of this study on the vaccination response of older individuals with diabetes arises from two main issues. On one hand, as mentioned above, diabetes is one of the chronic conditions that has been independently associated with higher severity of SARS-CoV-2 infection. As proof of this issue, in our sample, the residents without diabetes seemed to have an increased frequency of previous SARS-CoV-2 infection, but this was likely driven by the higher mortality of COVID-19 in individuals with diabetes. Therefore, patients with diabetes comprise one of the groups of individuals most likely to benefit from vaccination. On the other hand, however, previous studies have underlined the possible role of diabetes in modifying the effectiveness and extent of immune response to various vaccines (15). In most studies, individuals affected by diabetes demonstrated reduced immune response to hepatitis B vaccination, whereas no differences emerged regarding the influenza vaccine (15). Han et al. (31), in particular, observed an acceptable capacity to induce immunogenicity after hepatitis B vaccination in individuals with diabetes, although they had lower antibody levels than their counterparts without diabetes. Regarding pneumococcal vaccination, two studies reported no differences in the antibody response between participants with versus without diabetes for pneumococcal polysaccharide vaccines 13 and 14 (32,33), whereas Beam et al. (34) described a weaker antibody response in individuals with diabetes to serogroups 14, 18, and 23 (35,36). Nonetheless, adults with diabetes vaccinated against influenza and pneumococcal infection showed reduced clinical complications, hospitalizations, and mortality (37).

The literature is very limited on data regarding antibody response to SARS-CoV-2 vaccination in older individuals with diabetes and has shown conflicting results. The CAVEAT study tested whether glycemic control could affect antibody response to SARS-CoV-2 vaccination and found that poor glycemic control during the vaccination period led to worse antibody response, whereas individuals with diabetes with good glycemic control responded equally to those without diabetes (19). Mechanisms related to the lower response to vaccination in older individuals with diabetes may include hyperglycemia-related deficits in the immune system. For instance, hyperglycemia is associated with suppression of cytokine production; defective leukocyte recruitment and pathogen recognition; dysfunction of neutrophils, macrophages, and monocytes; reduced germinal centers; and lower production and function of antibodies (9,38). However, two recent studies did not observe any substantial role of glycemic control on immunologic response after vaccination during a shorter observation period compared with our study (16,17). Furthermore, maintaining satisfactory glycemic control is not easy to achieve in older patients with diabetes, because the risk of either hypo- or hyperglycemia is substantial, and addressing strict glycemic targets of HbA_{1c} levels has shown to be more detrimental in older frail compared with younger adults (39), with special challenges in LTCFs (40).

The findings from our study have underlined that immune response over 2- and 6-month observation periods from the first vaccine dose was similar in residents with diabetes using insulin compared with those without diabetes. Insulin therapy could be considered a proxy of diabetes duration and severity. However, previous studies have demonstrated that insulin influences adaptive immune function, and fewer but relevant works have also shown a possible impact on T cells (9). In this regard, some authors found that, despite presenting with increased leukocyte counts, individuals with type 2 diabetes were more likely to be lymphopenic and have a higher number of senescent $CD4^+$ and $CD8^+$ T cells (41). These cells were characterized by overexpressing chemokines (especially the C-X-C motif chemokine receptor type 2) and demonstrated altered migratory capacity (41), which may contribute to diabetes-related immune dysfunction and poorer vaccine response. In addition, diabetes was associated with higher apoptosis rates in T cells, resulting in lower circulating cell levels. However, in animal models, insulin therapy substantially attenuated the

Table 2—Linear mixed model for association between presence of diabetes and antidiabetic treatment and antibody levels over 6 months

	β coefficient (95% CI) *P* value	
	Model 1	Model 2
Presence of diabetes		
Diabetes (vs. no diabetes)	0.15 (0.03, 0.28)	0.15 (0.03, 0.27)
	0.01	**0.02**
Diabetes * time		
Diabetes * T1	−0.20 (−0.34, −0.06)	−0.20 (−0.34, −0.06)
	0.006	**0.005**
Diabetes * T2	−0.22 (−0.37, −0.07)	−0.22 (−0.37, −0.07)
	0.004	**0.004**
Presence of diabetes and ongoing treatment		
Diabetes with no insulin therapy (vs. no diabetes)	0.24 (0.08, 0.40)	0.24 (0.08, 0.39)
	0.003	**0.003**
Diabetes with insulin (vs. no diabetes)	0.11 (−0.09, 0.30)	0.11 (−0.08, 0.31)
	0.28	0.25
Diabetes * T1 (ref: no diabetes * T0)		
Diabetes with no insulin therapy * T1	−0.24 (−0.42, −0.05)	−0.24 (−0.43, −0.05)
	0.01	**0.01**
Diabetes under insulin * T1	−0.18 (−0.41, 0.05)	−0.18 (−0.41, 0.05)
	0.12	0.12
Diabetes * T2 (ref: no diabetes * T0)		
Diabetes with no insulin therapy * T2	−0.30 (−0.50, −0.10)	−0.30 (−0.50, −0.10)
	0.003	**0.003**
Diabetes with insulin * T2	−0.11 (−0.36, 0.13)	−0.11 (−0.36, 0.13)
	0.38	0.36

Bold font indicates significance. Model 1 includes age, sex, previous COVID-19 infection, and vaccine doses received. Model 2 also includes ethnicity, type of COVID-19 vaccine, mobility level, cognitive disorders, and number of chronic diseases. Random intercept models with effects nested within study site and individuals were performed. A total of 481 (for analysis considering presence of diabetes as main exposure) and 452 participants (for analysis considering both presence of diabetes and ongoing therapy as main exposure) had at least two assessments of humoral immunity. T0, prevaccination assessment; T1, 2 months after the first vaccine dose; T2, 6 months after the first vaccine dose.

number of apoptotic lymphocytes (22), suggesting a protective effect of this hormone in acquired immunity. One of the possible mechanisms through which insulin might positively influence the number and function of lymphocytes concerns magnesium homeostasis. In fact, in vitro studies have shown that insulin can increase intracellular ionized magnesium concentration in human lymphocytes (42) and may therefore prevent the establishment of intracellular Mg^{2+} deficits, which harm adaptive and acquired immunity (43).

We also found that older residents with diabetes using diet alone or antidiabetic oral agents showed weaker immune response over time compared with those without diabetes. This association was consistent after adjusting the analyses for specific chronic conditions or factors associated with frailty (e.g., mobility level, cognitive disorders, and multimorbidity) and when focusing only on nonfrail individuals, suggesting an independent role of diabetes.

Our study suggests that the negative impact of diabetes in determining a steeper antibody decline was greater in female residents than in male residents. These results could have partly been affected by the smaller number of male participants. However, they could also be explained by the greater clinical complexity of older men compared with women, which may obscure the independent effect of single conditions, such as diabetes. Moreover, our data could corroborate the presence of sex differences in vaccine response in advanced age, which might be linked to sex hormone variations and seem specific to vaccine type (29). For instance, older women reported a quantitatively (but not qualitatively) greater antibody response after influenza vaccination than men. Conversely, higher IgG concentrations were found among men for pneumococcal, tetanus, and diphtheria vaccines (29). Whether diabetes may interact with sex in influencing the extent and persistence of vaccine response is still unknown. In fact, of the studies that evaluated the immunogenicity of various vaccines in patients with diabetes (44), one study reported a similar response to the hepatitis B vaccine between adult men and women (45), and another observed higher IgG titers in women (46), whereas a majority did not investigate possible sex-related differences.

To our knowledge, this is the first study evaluating the immune response to SARS-CoV-2 vaccination as a function of diabetes in a population of vulnerable older residents of LTCFs. This was a large multicenter study in which we were able to collect clinical variables and immune response data in older individuals in LTCFs. Our study does have some limitations. First, we did not specifically collect data on glycemia or HbA_{1c} levels, so we could not evaluate diabetes control or severity at the time of data collection. Nonetheless, it is less likely that this issue affected diabetes diagnosis determining possible misclassification bias, because the ascertainment of diabetes was done by physicians based on residents' medical history, drugs used, and routine biochemical analyses (performed generally at admission in LTCFs and at least every 6 months and periodically based on clinical need). Second, our sample included older individuals in LTCFs, and a majority were Caucasian (97.3%). Therefore, our results can be generalized to older residents in LTCFs and might not be representative of the general population. Moreover, we could not explore any ethnicity-related differences in the studied association. Third, our study sample size was relatively small, especially concerning the number of residents with diabetes, and did not allow us to evaluate changes in humoral response between individuals receiving different oral antidiabetic agents and focus more on the sex differences in this issue. Future investigations are needed to verify and confirm our findings in larger cohorts of free-dwelling men and women with diabetes and in those belonging to other age and ethnic groups. Lastly, we did not assess in our analyses the risk of SARS-CoV-2 infection during the observation period. Indeed,

humoral response to vaccination might only in part explain the risk of contracting the infection, and other relevant factors (e.g., virus exposure and cell-mediated immunity) can play a role in determining this risk.

In conclusion, our study suggests that immunization against SARS-CoV-2 after vaccination in older residents in LTCFs is reduced in those with type 2 diabetes and that insulin therapy may buffer this effect.

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