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Posted Date: 2 November 2023

doi: 10.20944/preprints202311.0182.v1

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Article

BNT162b2 Booster Dose Elicits a Robust Antibody Response in Subjects with Abdominal Obesity and Previous SARS-CoV-2 Infection

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Abstract: Little is known about the long-term durability of the induced immune response in subjects affected by obesity, particularly in those with an abdominal distribution of adipose tissue. We evaluated SARS-CoV-2-specific antibody response after BNT162b2 vaccine booster dose, comparing individuals with abdominal obesity (AO) with those without, discerning between individuals previously infected or not. IgG-TrimericS were measured in 511 subjects at baseline, 21 days after vaccine dose-1 and at one, three, six and nine months after dose-2 and at one and three months after booster dose. Nucleocapsid antibodies were assessed at baseline and at the end of the study to detect SARS-CoV-2 infection. To evaluate the three-months difference in absolute variation of IgG-TrmicericS levels from booster dose we used multivariable linear regression that showed interaction between AO and SARS-CoV-2 infection status (p=0.016). AO is associated with higher absolute IgG-TrimericS variation in prior infected individuals, regardless of possible confounders and IgG-TrimericS levels at booster dose (p=0.0125). No interaction was evinced using BMI in the same regression model (p=0.418). The robust response in the development of antibodies after booster dose, observed in people with OA and previous infection, may support the recommendations to undergo the booster dose also in this population group.

Keywords: abdominal obesity; obesity; BMI; BNT162b2 mRNA vaccine; antibody response; IgG-TrimericS; booster dose; COVID-19

1. Introduction

The risk of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and the risk of developing major complications from coronavirus disease 2019 (COVID-19) is increased in people with chronic medical conditions [1]. Individuals with obesity, and particularly those with

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predominant visceral adipose tissue accumulation, are at significant risk of developing a more severe case of COVID-19 [2–4].

The approved SARS-CoV-2 messenger RNA (mRNA) vaccines are highly effective at reducing infection and morbidity in the general population and have been recommended for individuals with obesity [5]. People affected by obesity, in particular at a visceral level, are hypothesized to be predisposed to poor immunological responses to various vaccinations due to their chronic inflammatory state and immune dysregulation as well as other related comorbidities [4,6,7]. However, as of today, the efficacy of vaccines is reported not to be significantly different in people with and without obesity [5,8]. Therefore, people with obesity should be encouraged to undergo vaccination with any one of the currently available vaccines [5]. However, the impact of obesity and abdominal obesity (AO) on the durability of mRNA vaccine-specific responses remains an open question [9,10].

We and others previously reported a weaker immune response after two doses of BNT162b2 mRNA vaccine Pfizer-BioNTech and a greater drop in antibody levels at three months after dose-2 in infection-naïve subjects with AO compared to those without [11–13]. Therefore, the observed reduction in antibody levels over time after vaccination and the increase in positive cases led to the need for additional booster vaccination [11,14–17].

Little is known about the long-term durability of the induced immune response resulting from the vaccination and the response after a booster dose, especially in patients with AO. In addition, uncertainties remain regarding the impact of vaccination of previously infected individuals, with preliminary data showing higher antibody titres in those who were infected [18–22].

To this end, we evaluated SARS-CoV-2 specific antibody responses after the booster dose of the BNT162b2 mRNA vaccine in a large cohort of health care workers. We compared the response of individuals with AO with the response of those without AO, discerning their infection status (infection-naïve individuals and individuals infected pre or post vaccination cycle).

2. Material and methods

2.1. Study design and population

VARCO-19 study is an observational prospective cohort study started in January 2021 and ended in March 2022. All participants provided written informed consent. The protocol was approved by Ethics Committee of IRCCS-Lazzaro-Spallanzani (protocol code 48/2021/spall/PU/403-2021). The vaccination itself was not part of the study.

We collected blood samples from a cohort of health care workers who received up to three doses of BNT162b2 mRNA vaccine at the IRCCS Policlinico San Donato, a large academic medical centre in Milan, Italy. A description of the enrolment process and inclusion criteria was previously reported [11].

Study timeline is showed in Figure 1.

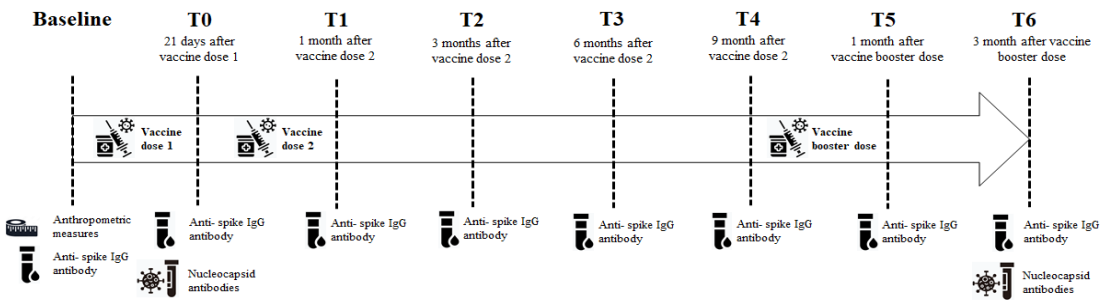

Figure 1. Study timeline. This figure shows all the events of the study.

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2.2. Serological testing

Serological testing was previously described [11]. Antibody levels were measured at eight time points: at baseline, at day 21 after vaccine dose 1 and at one (within 30-40 days), at three (within 90-100 days), at six (within 180-200 days) and nine months (within 270-280 days) after dose 2. Antibody levels were measured also after one (within 30-40 days) and three months (within 90-100 days) after booster dose. In this study, whether an antibody determination was above the upper limit of the assay range, a 1:20 dilution with specific LIAISON® TrimericS IgG Diluent Accessory buffer (DiaSorin, Italy) was used. Due to the limit of the linear range at the 1:20 dilution, sporadic titers of >40000 BAU/mL were obtained. Since the occurrence of that event was uncommon, no further dilutions were performed, and a titer of 40000 BAU/mL was assigned to those specimens. Qualitative assessment of anti-Nucleocapsid IgGs (anti-N IgG) was performed at the beginning of the study in order to screen if SARS-CoV-2 infections had occurred before vaccination. At the end of the observation period, anti-N IgG titer was determined again to evaluate whether a participant was infected with SARS-CoV-2 during the vaccination campaign.

2.3. Anthropometric measures

Anthropometric parameters were assessed at baseline. Waist circumference was measured midway between the lower rib and the iliac crest to the closest 1.0 cm. AO was defined as a waist circumference ≥102 cm in men and ≥88 cm in women [23]. Body weight was measured to the nearest 0.1 kg using a balance beam scale, height was measured to the nearest 0.1 cm using a stadiometer. Body mass index (BMI) was calculated as weight (kilograms) divided by height (meters) square.

2.4. Statistical analyses

We expressed antibody levels as geometric mean (±standard deviation, SD). Subjects were categorized according to AO esity and BMI classes with or without a prior SARS-CoV-2 infection diagnosis (no prior infection, infection diagnosis before vaccine or infection diagnosis after vaccine). For comparing between-group continuous values, the nonparametric Kruskal-Wallis test was used. We used multivariable linear regression to account for possible confounding and to evaluate the three-months difference in absolute variation of titre levels starting from booster dose in individuals with and without AO (or BMI-classes). The model was also adjusted for booster dose antibody levels, gender, age, smoke, hypertension and prior SARS-CoV-2 infection diagnosis and the interaction between prior infection and AO (or BMI-classes). Least-square (LS) means (±standard error, SE) were reported. The null hypothesis will be refused with $p < 0.05$. All statistical analyses were done with SAS version 9.4 (SAS Institute, Cary, NC).

3. Results

The initial study population consisted of 1060 employees of the IRCCS Policlinico San Donato, who received BNT162b mRNA vaccine and who provided at least one blood sample for antibody testing. Vaccine recipients were aged 41.4±12.9 years, 62% were female, and 93% were Caucasian: 1060 vaccine recipients (240 with prior infection) provided samples at day 21 after vaccine dose 1, at one month (within 30-40 days), at three months (within 90-100 days) after dose 2; 977 (218 with prior infection) provided samples at six months (within 180-200 days) after dose 2; 778 (177 with prior infection) provided samples at nine months (within 270-280 days) after dose 2; 571 (126 with prior infection) provided samples at one month (within 30-40 days) after booster dose; 511 (109 with prior infection) provided samples at three months (within 90-100 days) after booster dose, Figure 2.

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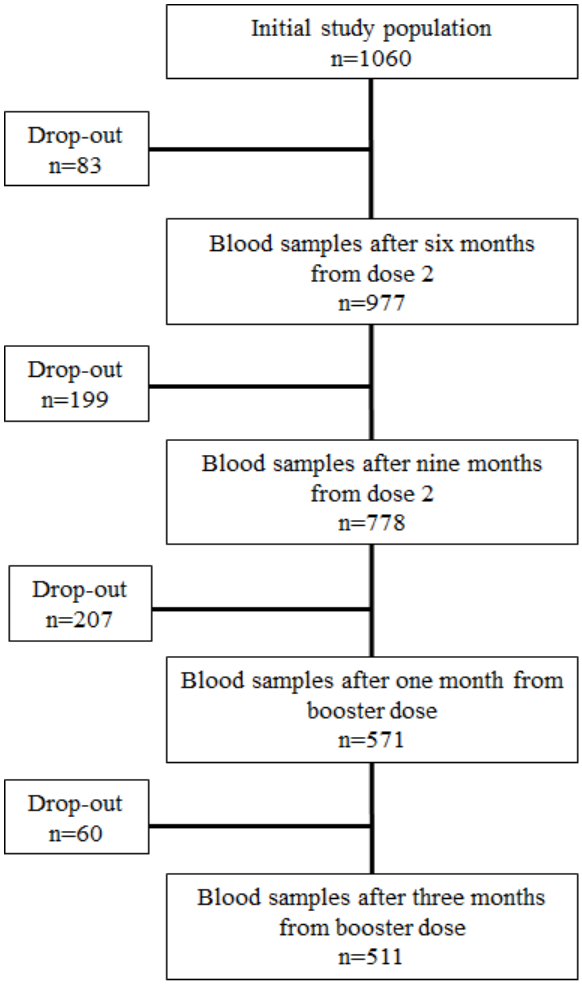

Figure 2. Study population flow diagram.

A total of 511 individuals provided blood samples at all-time points and were included in this analysis. Baseline characteristics of patients are reported in Table 1.

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Table 1. Demographic and clinical characteristics of all study population with or without abdominal obesity according to infection status.

		Abdominal Obesity (n=149)				No Abdominal obesity (n=362)			
	Total (n=511)	**No Prior SARS-CoV-2 infection (n=76)**	**Prior SARS-CoV-2 infection (n=34)**	**SARS-CoV-2 infection after vaccine**	**p-value**	**No Prior SARS-CoV-2 infection (n=186)**	**Prior SARS-CoV-2 infection (n=75)**	**SARS-CoV-2 infection after vaccine (n=101)**	**p-value**
Age, years	44.03±11.88	52.02±10.64	47.26±9.18	48.26±8.28	0.0286	42.28±12.02	41.73±11.20	40.15±11.70	0.3386
Race									
Caucasian	492 (96.28)	72 (94.74)	31 (91.18)	36 (92.31)		181 (97.31)	71 (94.67)	101 (100.00)	
Latin-American	13 (2.54)	3 (3.95)	3 (8.82)	3 (7.69)	0.7117*	2 (1.08)	2 (2.67)	0 (0.00)	0.2074*
African	2 (0.39)	0 (0.00)	0 (0.00)	0 (0.00)		2 (1.08)	0 (0.00)	0 (0.00)	
Arabic	4 (0.78)	1 (1.32)	0 (0.00)	0 (0.00)		1 (0.54)	2 (2.67)	0 (0.00)	
Gender									
Male	166 (32.49)	30 (39.47)	8 (23.53)	14 (35.90)	0.2656	56 (30.11)	28 (37.33)	30 (29.70)	0.4271
Female	345 (67.51)	46 (60.53)	26 (76.47)	25 (64.10)		130 (69.89)	47 (62.67)	71 (70.30)	
Smoking status									
Smoker	98 (19.18)	11 (14.47)	4 (11.76)	10 (25.64)	0.2128	36 (19.35)	11 (16.67)	26 (25.74)	0.1794
Non smoker	413 (80.82)	65 (85.53)	30 (88.24)	29 (74.36)		150 (80.65)	64 (85.33)	75 (74.26)	
Comorbidities									
Hypertension	59 (11.55)	25 (32.89)	7 (20.59)	6 (15.38)	0.0944	12 (6.45)	3 (4.00)	6 (5.94)	0.7435
Diabetes mellitus	4 (0.78)	0 (0.00)	2 (5.88)	0 (0.00)	0.0509*	0 (0.00)	1 (1.33)	1 (0.99)	0.2357*
Cardiovascular	17 (3.33)	6 (7.89)	0 (0.00)	1 (2.56)	0.2318*	7 (3.76)	1 (1.33)	2 (1.98)	0.5268*
Dyslipidemia	32 (6.26)	9 (11.84)	4 (11.76)	5 (12.82)	1.000*	7 (3.76)	3 (4.00)	4 (3.96)	1.000*
Cancer	3 (0.59)	1 (1.32)	0 (0.00)	1 (2.56)	1.000*	1 (0.54)	0 (0.00)	0 (0.00)	1.000*
Anthropometric									
Weight, kg	70.54±15.12	84.08±13.74	88.28±16.96	80.86±14.45	0.1026	64.38±11.15	65.40±12.29	65.53±10.23	0.6481
Height, cm	167.63±8.78	168.47±10.54	166.14±9.01	167.21±8.61	0.4903	166.91±8.39	168·21±8.65	168.56±8.10	0.2252
Waist, cm	85.78±13.51	100.69±8.76	103.26±11.23	99.79±9.47	0.2745	79.61±9.20	76.63±9.23	79.19±9.22	0.9254

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Waist male, cm	94.63±11.85	107.25±5.64	112.88±9.79	107.93±6.56	0.1104	89.26±7.47	87.38±7.93	87.75±7.91	0.4994
Waist female, cm	81.52±12.13	96.41±7.74	100.31±10.05	95.24±7.64	0.0751	75.46±6.31	75.02±6.49	75.58±7.13	0.8975
WHtR	0.51±0.08	0.60±0.05	0.62±0.06	0.60±0.05	0.0589	0.48±0.05	0.47±0.05	0.47±0.05	0.5170
BMI, kg/m^2	25.00±4.45	29.53±3.28	31.79±4.39	28.81±3.76	0.00019	23.02±2.91	22.96±2.87	23.02±2.89	0.9869
BMI classes									
Underweight	20 (3.91)	0 (0.00)	0 (0.00)	0 (0.00)		12 (6.45)	2 (2.67)	6 (5.94)	
Normal weight	265 (51.86)	7 (9.21)	1 (2.94)	7 (17.95)	0.0951*	129 (69.35)	51 (68.00)	70 (69.31)	0.8376*
Overweight	156 (30.53)	34 (44.74)	13 (38.24)	20 (51.28)		43 (23.12)	22 (29.33)	24 (23.76)	
Obesity	70 (13.70)	35 (46.05)	20(58.82)	12 (30.77)		2 (1.08)	0 (0.00)	1 (0.99)	

*Fisher test. Abdominal obesity (waist circumference ≥102 cm for men, ≥88 cm for women); No abdominal obesity (waist circumference <102 cm for men, <88 cm for women); Underweight (BMI <18.5 kg/m^2); Normal weight (BMI from 18.5 to <25 kg/m^2); Overweight (BMI from 25 to <30 kg/m^2); Obesity (BMI≥30 kg/m^2). Body Mass Index (BMI); Waist-to-height ratio (WHtR); Other comorbidities (thyroid diseases, thyroid nodules, glaucoma, alopecia, depression, osteoporosis, kidney stones, gastritis, gastroesophageal reflux disease, irritable bowel syndrome, hallux valgus, carpal tunnel, diverticulosis, celiac disease, allergic asthma and anaemia); Antibody levels are expressed as BAU/mL (BAU = Binding Antibody Units) and are presented as geometric mean [95% confidence interval]. Data are n (%), mean (SD).

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We divided our sample according to two parameters: the presence of AO and infection status. According to waist circumference cut off, 149 subjects (29.1%) had AO and 362 (70.9%) had normal adipose tissue distribution. According to infection status, subjects were divided into three categories: 1) those who had never been infected with SARS-CoV-2 (infection-naïve individuals, n=262, 51.3%); 2) those who had developed the infection before the vaccine cycle (prior infected individuals, n=109, 21.3%); and 3) those who developed the infection during the vaccine cycle (post infected individuals, n=140, 27.4%). Figure 3 shows IgG-TrimericS antibody response to mRNA Sars-CoV-2 vaccination in individuals with or without AO according to infection status at all-time points.

3.1. Individuals who had never been infected with SARS-CoV-2 (Infection-naïve individuals)

Among infection-naïve individuals, n=262, 76 (29%) with and 186 (71%) without AO, between the third and ninth month after vaccine dose 2, there is a decrease in IgG-TrimericS levels in both subjects with AO and those without AO (0.22-fold [95% CI: 0.16-0.29] vs. 0.20-fold [95% CI: 0.17-0.23], respectively), Table 2, Figure 3. At one and three months after vaccine booster dose, IgG-TrimericS levels were lower in individuals with AO than those without AO without reaching statistical significance. An antibody peak was shown at one month after the vaccine booster dose (geometric mean BAU/mL ±standard deviation, 6470.55±695.82 BAU/ mL in individuals with AO vs 7561.64±406.80 BAU/ mL in individuals without AO, p=0.173), and a decline at the third month (2943.17±335.19 BAU/ mL in individuals with AO vs 3346.92±208.06 BAU/mL in individuals without AO, p=0.413), Table 2, Figure 3.

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Table 2. IgG-TrimericS Antibody Levels of subjects who provided a blood sample at all-time points stratified by the presence or absence of abdominal obesity and SARS-CoV-2 infection status.

		Abdominal Obesity (n=149)				No abdominal obesity (n=362)			
Antibodies levels	**Total (n=511)**	**No Prior SARS-CoV-2 infection (n=76)**	**SARS-CoV-2 infection before vaccine (n=34)**	**SARS-CoV-2 infection after vaccine (n=39)**	**p-value**	**No Prior SARS-CoV-2 infection (n=186)**	**SARS-CoV-2 infection before vaccine (n=75)**	**SARS-CoV-2 infection after vaccine (n=101)**	**p-value**
Baseline	9.67±1.40 n=90	4.81 n=11	98.93±74.44 n=6	4.81 n=8	<0.0001 *°	5.59±0.58 n=32	71.81±24.26 n=13	6.11±1.19 n=20	<0.0001 *°
21 days after dose 1	680.84±49.58	274.16±36.40	7511.83±1895.77	333.58±61.94	<0.0001 *°	362.54±26.99	7872.56±931.04	410.72±32.39	<0.0001 *°
1 month after dose 2	2837.32±110.30	1773.18±155.93	7420.51±1296.00	2130.24±231.39	<0.0001 *°	2399.17±123.48	6562.31±631.09	2386.67±156.08	<0.0001 *°
3 months after dose 2	1035.22±43.80	575.90±53.28	2985.81±550.26	672.12±68.08	<0.0001 *°	892.48±44.54	2868.23±308.43	820.87±60.84	<0.0001 *°
6 months after dose 2	463.96±21.32	267.78±14.63	1335.15±267.46	296.44±30.03	<0.0001 *°	391.60±22.71	1431.65±155.39	358.84±29.21	<0.0001 *°
9 months after dose 2	243.18±11.93	126.78±14.62	746.25±131.40	183.41±32.79	<0.0001 *°	176.38±10.74	847.73±92.92	216.88±17.25	<0.0001 *°
1 month after dose 3	6218.25±237.47	6470.55±695.82	6413.54±832.40	6850.16±947.21	0.8892	7561.64 ±406.80	4521.62±429.76	5084.36±500.43	<0.0001 #*
3 month after dose 3	4175.81±181.19	2943.17±335.19	4692.80±854.60	8791.71±1246.30	<0.0001 #°	3346.92±208.06	3345.35±314.00	6944.18±682.39	<0.0001 #°

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Abdominal obesity (waist circumference ≥102 cm for men, ≥88 cm for women); no abdominal obesity (waist circumference <102 cm for men, <88 cm for women). *(SARS-CoV-2 infection before vaccine vs No Prior SARS-CoV-2 infection) #(SARS-CoV-2 infection after vaccine vs No Prior SARS-CoV-2 infection) °(SARS-CoV-2 infection before vaccine vs SARS-CoV-2 infection after vaccine).

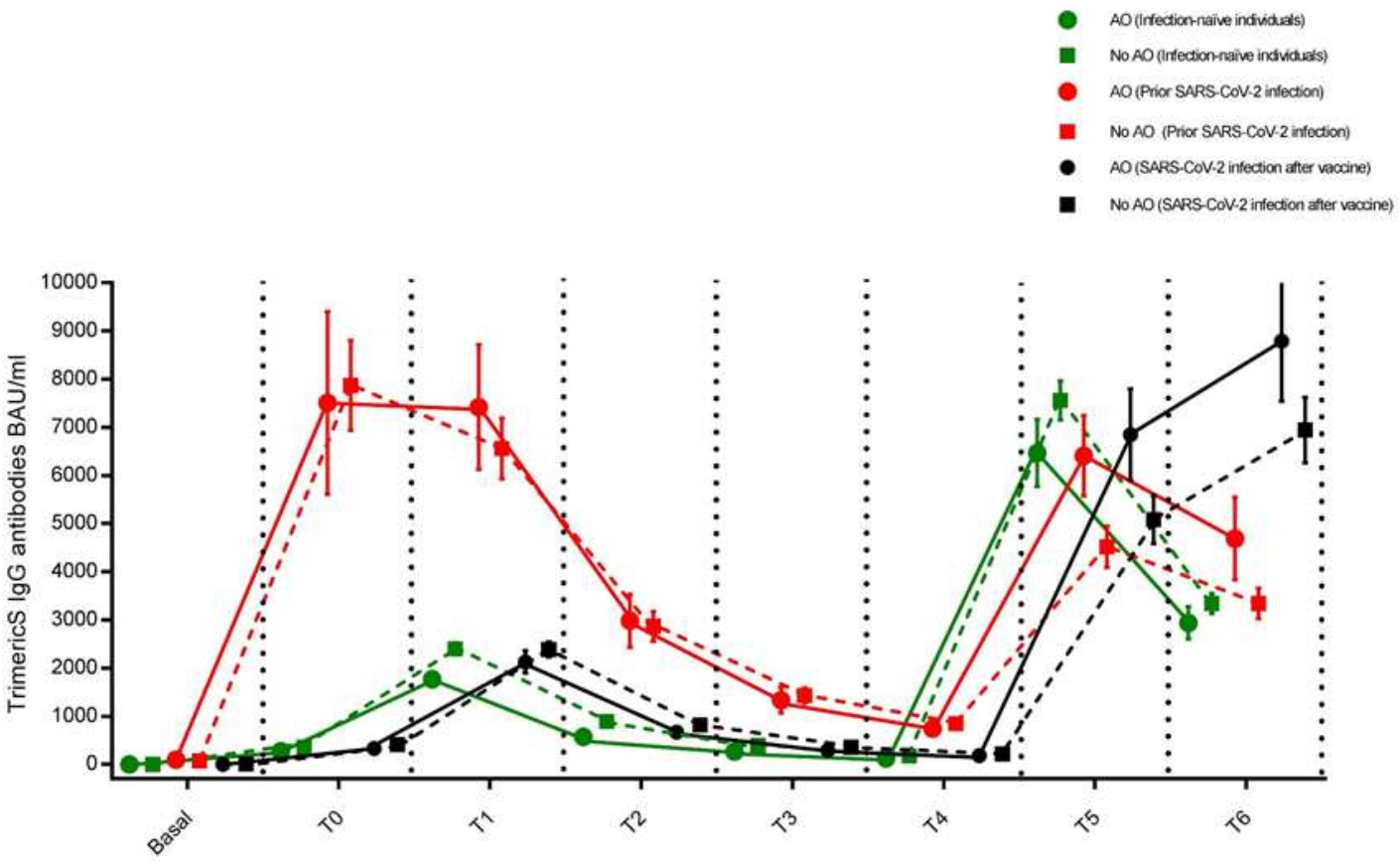

Figure 3. IgG-TrimericS antibody response to mRNA Sars-CoV-2 vaccination in individuals with or without abdominal obesity according to infection status. Infection-naïve individuals (green), individuals with prior infection (red) and individuals infected with SARS-CoV-2 after booster dose (black). Abdominal obesity (waist circumference ≥102 cm for men, ≥88cm for women); no abdominal obesity (waist circumference <102 cm for men, <88cm for women).

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3.2. Individuals who had developed the infection before the vaccine cycle (Prior infected individuals)

Among prior infected individuals, n=109, 34 (31.2%) with and 75 (68.8%) without AO, between the third and ninth month after vaccine dose 2, the drop in IgG-TrimericS levels is remarkable in both subjects with AO and those without AO (0.25-fold [95% CI: 0.15-0.42] vs. 0.20-fold [95% CI: 0.30-0.33], respectively), Table 2, Figure 3.

At one month after vaccine booster dose, individuals with AO reached a higher peak of IgG-TrimericS levels than those without AO (6470.55±695.82 BAU/mL vs 4521.62±429.76 BAU/mL, p=0.0521). Between the first and the third month after vaccine booster dose, the drop in IgG-TrimericS levels was similar in individuals with or without AO (0.73 fold [95% CI: 0.48-1.14] vs 0.74 fold, [95% CI: 0.57-0.96], p=0.2352), Table 2, Figure 3.

3.3. Individuals who developed the infection during the vaccine cycle

One hundred and forty individuals, 39 (27.9%) with and 101 (72.1%) without AO, became positive for SARS-CoV-2 anti-nucleocapsid IgG antibodies testing at the end of the observation period, indicating that they had contracted COVID-19 during the vaccine cycle. The most observed symptoms were mild, ranging from asymptomatic to mild fever. Among individuals who presented symptoms (n=54), there were 38 (70.3%) individuals with AO and 16 (29.7%) individuals without AO. Between the third and ninth month after vaccine dose 2, there is a decrease in IgG-TrimericS levels in both subjects with AO and those without AO (0.27-fold [95% CI: 0.18-0.41] vs. 0.26-fold [95% CI: 0.21-0.3], respectively), similarly to infection-naïve individuals, Table 2, Figure 3. At one month after vaccine booster dose, individuals with AO showed similar IgG-TrimericS levels to those without AO (6850.16±947.21 BAU/mL vs 5084.36±500.43 BAU/mL, p=0.119). Also between the first and the third month after vaccine booster dose, they reached a higher peak of IgG-TrimericS levels than those without AO, even without statistical significance (8791.71±1246.30 BAU/mL vs 6944.18±682.39 BAU/mL, p=0.242), Table 2, Figure 3.

3.4. Multivariable linear regression analysis

Analysis of these data by multivariable linear regression to evaluate the three-months difference in absolute variation of IgG-TrimericS levels starting from booster dose showed evidence of interaction between AO and SARS-CoV-2 infection (p=0.016; Table 3). Specifically, AO is associated with higher absolute IgG-TrimericS variation in prior infected individuals, regardless of sex, age, hypertension or smoking, and IgG-TrimericS levels at booster dose (LS means 8432.09±1191.67 versus 5091.93±918.62, p=0.0125). No interaction was evinced using BMI classes in the same regression model (p=0.418).

Table 3. Univariate and multivariable linear regression (p-value) to evaluate the three-months difference in absolute variation of IgG-TrimericS antibody levels starting from booster dose.

	p-value		
	Univariate	**Multivariable considering abdominal obesity**	**Multivariable considering BMI class**
Sex	0.7120	0.5955	0.5656
Age	0.3000	0.4485	0.5412
IgG-TrimetricS antibody level at booster dose	0.0675	0.0855	0.0526
Prior SARS-CoV-2-infection	<0.0001	<0.0001	<0.0001
Abdominal obesity	0.1053	0.1092	-

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Interaction with prior SARS-CoV-2-infection Abdominal obesity*		0.0163	-
BMI classes	0.0803	-	0.0821
Interaction with prior SARS-CoV-2-infection BMI classes*		-	0.4176
Smoking status	0.0925	0.3785	0.2968
Hypertension	0.0062	0.0020	0.0063
Diabetes mellitus	0.5878		
Cardiovascular diseases	0.7262		
Dyslipidemia	0.5087		
Cancer	0.3900		

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); Abdominal obesity (waist circumference ≥102 cm for men, ≥88 cm for women); No abdominal obesity (waist circumference <102cm for men, <88cm for women); Body Mass Index (BMI): underweight (BMI <18.5 kg/m^2); normal weight (BMI from 18.5 to <25 kg/m^2); overweight (BMI from 25 to <30 kg/m^2); obesity (BMI≥30 kg/m^2).

4. Discussion

In our longitudinal observational study, we presented data about the antibodies levels up to twelve months after vaccination with two doses of BNT162b2 mRNA vaccine as well as following booster dose in a cohort of health care workers.

Consistent with other works, our results showed a peak in antibody levels value one month after the second dose of vaccine followed by a progressive decline until booster dose administration in subjects with or without AO who have never been infected with SARS-CoV-2 and in those who developed the infection before the vaccine cycle. Previous studies showed that humoral responses after the second dose of vaccination with COVID-19 vaccine decreased in all population groups approximately six months after the second dose of vaccine [15,24]. The decline in humoral responses does not depend on the type of COVID-19 vaccine administered but on host factors [11,12,25–28]. Overall, it has already been shown that the humoral immune response to vaccination differs significantly between individuals previously infected with SARS-CoV-2 and naïve individuals [29].

We found that in all infection-naïve individuals, IgG-TrimericS concentrations decreased steadily after nine months from the second dose and after three months from the booster dose of BNT162b2 m-RNA vaccine. Similarly to our previous work [11] and in according with other works [13,30], infection-naïve individuals with AO, at one and three months after vaccine booster dose, have lower antibody levels than individuals without AO, suggesting that the duration of vaccine-induced immunity may be reduced in people with obesity. In a previous work, Watanabe et al. showed that central obesity is associated with a reduced adaptive response to BNT162b2 m-RNA vaccine and that weight loss or improved metabolic health can reverse the effect [26]. Adipose tissue not only acts as a lipid store and energy source, but is also an endocrine organ that secretes fatty acids, metabolites, and adipokines that play an important role in inflammation and immune response [4,31–34]. In people with general obesity and AO, chronic inflammation, which develops as a result of dysfunctional adipose tissue, adversely affects T-cell functions, antibody response and macrophage migration [35–37]. This is due to an excessive accumulation of adipose tissue, particularly at the AO which can lead to the production of adipokines and proinflammatory cytokines, negatively affecting the immune response [31].

Therefore, immune dysfunction increases the risk of SARS-CoV-2 infection and decreases vaccine response in naïve individuals with severe obesity [36,38].

Our data showed that previously infected individuals with AO had higher concentrations of IgG-TrimericS levels at one month after vaccine booster dose than individuals without AO. This could be a result of severe infection that is more evident in patient with obesity [39,40].

 doi:10.20944/preprints202311.0182.v1

Previous research, in fact, has shown that the level of antibodies to COVID-19 is associated with disease severity and that patients with obesity have a higher risk of severe disease from COVID-19 [41,42]. Individuals with severe obesity who survived COVID-19 generated robust and durable SARS-CoV-2 specific T-cell immunity, a result of a severe infection that is more evident in patients with severe obesity [43,44]. In addition, Muena et al. showed that long-lasting neutralizing antibody responses induced by natural infection can be significantly enhanced after immunization with CoronaVac or BNT162b2 vaccines when administered up to 13.3 months after the onset of COVID-19 symptoms, suggesting that the infection induces a robust immune response [45]. The combination of a previous SARS-CoV-2 infection and vaccination, hybrid immunity, seemed to confer the greatest protection against SARS-CoV-2 infections [46,47]. It was showed that booster vaccination after natural COVID-19 infection provides a more sustained humoral immune response in terms of magnitude and quality than vaccination in infection-naïve individuals, fully consistent with clinical epidemiological observations [29]. This could explain the hyper-antibody response to the vaccine in this population as reflected in our results.

Our data show that 27.4% of our population contracted COVID-19 despite having undergone the vaccination cycle and having high antibody levels. However, none of these subjects showed severe symptoms, but only mild manifestations such as fatigue, cold, sore throat, low-grade fever and joint pain, suggesting that hybrid immunity could protect from a severe COVID-19 illness. These results are in line with a previous study who showed that hybrid immunity and booster vaccination are associated with a reduced risk and symptom number of SARS-CoV-2 infection [48]. When ignoring the booster, any additional protection of two dose vaccination in infection-naïve individuals was no longer observed [48]. Therefore, for infection-naïve individuals, booster vaccination might reduce the risk of a symptomatic SARS-CoV-2 infection, although this benefit seems to wane over time [48].

Limitations of our study include lack of measurement of virus-specific T cells. Anthropometric measurements were assessed only once. Furthermore, we did not evaluate proinflammatory markers of infection and do not know whether the vaccine BNT162b2 is protective against the Omicron XBB.15.

5. Conclusion

Abdominal obesity represents a risk factor for serious COVID-19 complications. As of today, the efficacy of COVID-19 vaccines is reported not to be significantly different in people with and without obesity. Our findings showed a robust response in the development of antibodies against COVID-19 after BNT162b2 booster dose in people with AO who had already come into contact with the virus. Our results further support recent recommendations to offer "booster" vaccines to adults with high-risk medical conditions, including obesity, and, particularly, to those with a more prevalent AO phenotype.

Author Contributions: Conceptualization, A.E.M. and C.D.; methodology, C.D., R.C., L.V.R.; formal analysis, V.M., S.B. and F.A.; investigation, A.E.M., C.D., C.M., L.V.R. and M.B.T.; resources, A.E.M., L.M., M.M.C.R. and R.C.; data curation, C.D. C.M. and M.B.T.; writing—original draft preparation, A.E.M., C.D. and C.M.; writing—review and editing, A.E.M., C.D., C.M., C.B. (Caterina Bertolini), C.B. (Carola Buscemi), V.S., M.T.C., E.C., C.R., M.C., G.I., E.N.; funding acquisition, A.E.M.

Funding: This study was partially supported by Ricerca Corrente funding from the Italian Ministry of Health to IRCCS Policlinico San Donato and by GSD Foundation.

Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Ethics Committee of the IRCCS Lazzaro-Spallanzani (protocol code 48/2021/spall/PU/403–2021).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available upon request from the corresponding author.

Acknowledgments: The authors acknowledge all the staff of IRCCS Policlinico San Donato. A special mention for all the nurses of IRCCS Policlinico San Donato for the precious help in blood sample collection. Finally, the authors would like to thank Sara Basilico, Michele Iovane and Gloria Capitanio for the time and the effort placed into this study.

Conflicts of Interest: The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

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