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The Impact of Body Fat Distribution on COVID-19 Vaccine Response: An MRI-Based Study

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ABSTRACT

Objective: Subcutaneous and visceral adipose tissue have distinct physiological roles. The correlation between the amount of visceral tissue and the immunity response following vaccination remains unclear, despite its known effects on immunity. The purpose of this study is to examine the relationship between SARS-CoV-2 IgG antibody levels after vaccination and body fat tissue values measured using a specialized software on specific magnetic resonance imaging sequences.

Methods: After ethics committee approval, prospectively 60 volunteers (27 males, 33 females; median age of 33 years) were vaccinated with inactivated SARS-CoV-2 vaccine and tested for IgG levels. Abdominal MRI was performed to measure subcutaneous and visceral fat tissue areas using a semiautomatic application.

Results: The median value of IgG antibody titers after vaccination was 1039 (113 – 6613). Median subcutaneous adipose tissue(cm^2), visceral adipose tissue (cm^2), SAT index (SATI) (cm^2/m^2), VAT index (VATI) (cm^2/m^2), total fat area (TFA) (cm^2), and SAT/VAT (cm^2) were 178.5 (38.1-552.5), 51.5 (7.1-273.2), 61.4 (14.3-213.1), 19.1 (2.7-90.6), 251.3 (45.3-683.2), and 3.3 (0.4-12.3) respectively. There was no significant correlation between the adipose tissue measurements and antibody titers (p>.05).

Conclusion: This study demonstrated that automated software can efficiently and accurately evaluate body fat distribution using MRI. However, the results showed no significant association between fat distribution and the immunization response to the SARS-CoV-2 vaccine.

Keywords: Covid-19, CoronaVac, SinoVac, body fat distribution, Magnetic Resonance Imaging

1. INTRODUCTION

Obesity is a significant risk factor for respiratory infection during the COVID-19 pandemic caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) (1). It has been proposed that adipose tissue-related systemic inflammatory response plays a role in the pathophysiology of this condition (1,2). Obesity-related inflammation and impaired pathogen response in obese individuals have been the subject of research for many years (3–5).

While studies have traditionally used body mass index (BMI) data as a measure of overall adipose tissue, it is now recognized that obesity is a heterogeneous disease group. It is known that visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) show significant differences in their characteristics. For this reason, body fat distribution is detailed by calculating VAT and SAT values (6). VAT has more inflammatory and immune cells than SAT, but has less preadipocyte differentiation capacity (6).

As of December 2022, the ongoing COVID-19 pandemic has affected 396 million people worldwide and caused the death of 6.6 million people (7). Efforts to develop vaccines to control the pandemic are ongoing, and there are many vaccines currently in clinical trials or in use. One of them, CoronaVac, is an inactivated SARS-CoV-2 vaccine produced by Sinovac Life Sciences (Beijing, China).

The vaccines are being applied to a broader population every day, and the rates and duration of immunity in vaccinated individuals are being studied. Age, gender, smoking, drinking, obesity, and immunity status are among the main factors that may affect immunization and its continuity. Studies have shown that obese patients have a poor response to vaccines and produce lower antibody titers to different vaccine types (8,9).

In this prospective study, obesity was quantified by calculating the body fat distribution based on VAT and SAT values. Antibody response to the CoronaVac vaccine was measured

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by spike glycoprotein antibody titers, and the relationship between obesity and antibody titers after vaccination was investigated.

2. METHODS

2.1. Study Design and Subjects

This study is a single-center, prospective observational study. Written informed consent was obtained from each participant before enrolment. The Ethics Committee (2021/90-1322) approved the clinical trial protocol and informed consent form.

This study was conducted among healthcare workers who received the CoronaVac vaccine. The study included sixty adult volunteers aged 18 or older, with a median age of 33 years (27 males and 33 females). All participants received two doses of the vaccine and were tested for SARS-CoV-2 IgG levels. In addition, they underwent abdominal magnetic resonance imaging (MRI) to measure fat tissue related parameters. Participants with immunosuppression, a history of taking immunomodulatory or immunosuppressive drugs, previous COVID-19 infection, or contraindications for MRI were excluded from the study.

2.2. CoronaVac vaccination and SARS-CoV-2 IgG detection

CoronaVac is an inactivated SARS-CoV-2 vaccine (Sinovac Life Sciences, Beijing, China). 0.5 ml CoronaVac vaccine containing 600 SU antigens, maintained at +20 to +80 degrees, was administered intramuscularly in 2 doses with 28-day intervals. The first dose was administered on January 16, 2021, and the second dose was administered on February 13, 2021. SARS-CoV-2 IgG (spike glycoprotein) levels were tested 14-21 days after administration of the second dose of the vaccine.

SARS-CoV-2 IgG II Quant (Abbott, Ireland Diagnostics Division, Finisklin Business Park, Sligo, Ireland) test is used clinically to diagnose SARS-CoV-2 and evaluate the immune status of individuals by measuring antibodies against the spike protein of SARS-CoV-2. This test kit uses the chemiluminescent microparticle immunoassay (CMIA) method to qualitatively and quantitatively determine the presence of IgG antibodies against SARS-CoV-2 in human serum and plasma. The test was performed on the Abbott ARCHITECT plus ci4100 device following the manufacturer's recommendations, with a cut-off value of ≥50 AU/ml.

2.3. Abdominal Magnetic Resonance Imaging

All MRI exams were performed at a single center with a 1,5T MR scanner (Magnetom Aera, Siemens Erlangen, Germany). A sixteen-element phased abdominal coil (16-channel coil) was used. Participants were imaged during a single breath-hold after expiration in the supine position, and GE T1 Dixon Fat Only sequences were obtained. (FOV 380 mm, matrix 240x380 mm, TR 6.64 ms, TE 2.39 ms, slice thickness 2.5 mm, gap 1.0 mm, NEX 1). It took averagely 15 seconds to obtain the sequence for each volunteer.

2.4. Fat Tissue Quantification

A single acquisition with the GE T1W Vibe Dixon sequence can generate four image series: in-phase, out-of-phase, water-only, and fat-only. The analysis was performed on the fat-only image series from a single slice at L3 vertebral level. The intensity inhomogeneities that can occur in MR imaging due to tissue differences, magnetic field variations, devices, and coil types make it difficult to determine a standard signal value in MR images. Therefore, while measurements can be made with standardized Hounsfield unit levels in CT imaging, it is not possible to determine a standard signal value in MR images (10). Many methods are described to reach quantifiable standard data by eliminating the problem of signal inhomogeneity in images (11–14). Classifying voxels has an important place among these methods, and the two most used classification methods are; k-means clustering and fuzzy c-means clustering methods.

The study was conducted with the ImageJ application, an image processing program produced by NIH, and FATCALC, which works as a macro plugin of this application (15,16). FATCALC software provides VAT and SAT tissue segmentation and quantification after processing images with multiple algorithms. The algorithm of statistical region merging (SRM) and the spatial fuzzy c-means clustering (SFCM) are used in this software. The technical details of the software are explained widely in the paper of Maddalo et al. (16).

In the fat-only Dixon MR images, the section corresponding to the L3 vertebra level was determined, and VAT and SAT tissue areas were calculated as cm^2 by using FATCALC software. The software allows manual editing after the automatic calculations are done, and the radiologist modifies the minor errors if necessary. Fig. 1 shows an example of axial fat-only Dixon MR image and VAT and SAT segmentation by FATCALC.

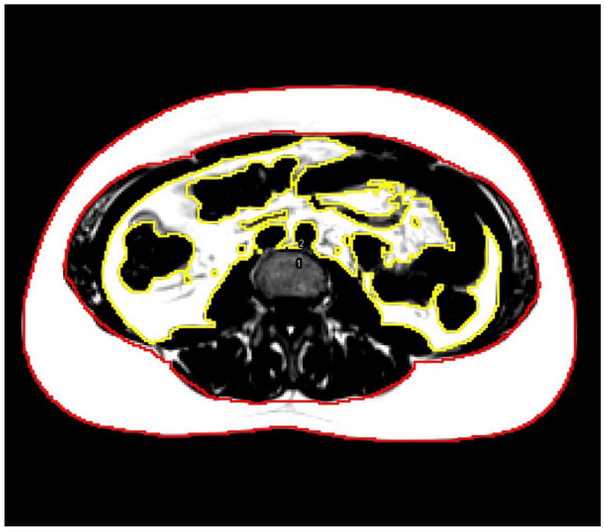

Figure 1. *Example of axial fat-only Dixon MR image and VAT and SAT segmentation by FATCALC. In the axial fat-only Dixon MRI image obtained from the level of the L3 vertebral body, subcutaneous and visceral fat tissues can be easily distinguished. FATCALC software automatically selected areas of adipose tissue (red contoured area, subcutaneous adipose tissue; yellow contoured areas visceral adipose tissue).*

2.5. Statistical Analysis:

Subcutaneous adipose tissue area (SAT, cross), Visceral adipose tissue area (VAT), subcutaneous adipose tissue index (cross-sectional areas (cm^2) of SAT, normalized by the square of one's height (m^2)), visceral adipose tissue index (cross-sectional areas (cm^2) of VAT, normalized by the square of one's height (m^2)), subcutaneous adipose tissue/visceral adipose tissue ratio (SAT/VAT), Total fat area (SAT+VAT) values were obtained for statistical analysis.

Mean, standard deviation, median, minimum, maximum value frequency, and percentage were used for descriptive statistics. The distribution of variables was checked with the Kolmogorov-Smirnov test. Mann-Whitney U tests were used to compare quantitative data, and the Chi-Square test was used to compare the qualitative data. The significance level was set at 5% ($P \leq .05$). SPSS 27.0 was used for statistical analyses.

3. RESULTS

Sixty healthy healthcare worker volunteers were included in the study. The baseline characteristics of the volunteers are summarized in Table 1. Of note, the median age of volunteers was 33 years (23-58), the female-male distribution was 33-27 (55%-45%), the median BMI was 24.7kg/m^2 (16.9-35.9), and 32 (53.3%) had a BMI below 25kg/m^2, compared to 28 (46.7). %) was 25kg/m^2 or more. Median SAT (cm^2), VAT (cm^2), SATI (cm^2/m^2), VATI (cm^2/m^2), TFA (Total Fat Area, sum of SAT and VAT) (cm^2), and SAT/VAT (cm^2) were 178.5 (38.1-552.5), 51.5 (7.1-273.2), 61.4 (14.3-213.1), 19.1 (2.7-90.6), 251.3 (45.3-683.2), and 3.3 (0.4-12.3) respectively (Table 2).

Table 1. *Demographic characteristics of the volunteers*

Age (years)	
Median	33.0
Mean ± SD	35.2 ± 9.5
Range	23-58
Sex — no. (%)	
Male	27 (45.0)
Female	33 (55.0)
Smoking status — no. (%)	
Yes	13 (21.7)
No	47 (78.3)
Alcohol consumption — no. (%)	
Yes	39 (65.0)
No	21 (35.0)
Hypertension — no. (%)	
Yes	2 (3.3)
No	58 (96.7)
Diabetes Mellitus — no. (%)	
Yes	1 (1.7)
No	59 (98.3)
Cardiovascular disease — no. (%)	
Yes	2 (3.3)
No	58 (96.7)
SARS-CoV-2 spike antibody titers (AU/mL)	
Median	1039.0
Mean ± SD	1253.0 ± 1128.0
Range	113.0-6613.0
Height (m)	
Median	1.67
Mean ± SD	1.69 ± 0.09
Range	1.54-1.93
Weight (kg)	
Median	69.5
Mean ± SD	72.1 ± 15.8
Range	45.0-115.0
Body mass index (BMI) (kg/m^2)	
Median	24.7
Mean ± SD	25.1 ± 4.1
Range	16.9-35.9
< 25 — no. (%)	32 (53.3)
≥ 25 — no. (%)	28 (46.7)

Table 2 *Summary statistics of each body composition according to spike antibody titers.*

Variables	All	≤ 1000 (AU/mL)	> 1000 (AU/mL)	*P* value
Age Median Mean ± SD	33.0 35.2 ± 9.5	33.0 36.0 ± 9.9	33.0 34.5 ± 9.3	.589
Sex Male Female	27 (45.0%) 33 (55.0%)	15 (51.7%) 14 (48.3%)	12 (38.7%) 19 (61.3%)	.311
Height (m) Median Mean ± SD	1.67 1.69 ± 0.09	1.70 1.70 ± 0.09	1.65 1.68 ± 0.09	.260
Body mass index (BMI) (kg/m^2) Median Mean ± SD *< 25* *≥ 25*	24.7 25.1 ± 4.1 32 (53.3%) 28 (46.7%)	24.8 25.4 ± 4.2 15 (51.7%) 14 (48.3%)	24.5 24.7 ± 4.0 17 (54.8%) 14 (45.2%)	.690 .809
Subcutaneous adipose tissue area (SAT) (cm^2) Median Mean ± SD	178.5 180.8 ± 84.0	169.5 171.0 ± 93.4	186.3 189.9 ± 74.6	.171
Visceral adipose tissue area (VAT) (cm^2) Median Mean ± SD	51.5 84.0 ± 73.4	51.9 86.1 ± 71.8	51.2 82.0 ± 76.1	.853
Total fat area (TFA) (cm^2) Median Mean ± SD	251.3 264.8 ± 129.5	238.2 257.1 ± 134.6	251.7 271.9 ± 126.4	.501
Subcutaneous adipose tissue index (SATI) Median Mean ± SD	61.4 63.9 ± 31.0	59.0 59.4 ± 34.9	70.1 68.0 ± 26.9	.063
Visceral adipose tissue index (VATI) Median Mean ± SD	19.1 28.8 ± 24.3	19.4 29.4 ± 24.6	18.8 28.2 ± 24.5	.853

Adequate antibody titers (≥50 AU/ml) were obtained after vaccination in all subjects participating in the study. The median value of IgG antibody titers was 1039 AU/ml and ranged from 113 AU/ml to 6613 AU/ml. The mean value of the titer data was calculated as 1000 AU/ml. Thus, statistical comparison was made by dividing the subjects into two groups with a titer value of ≤1000 AU/ml and >1000 AU/ml.

There was no statistically significant relationship between antibody titers and subcutaneous adipose tissue areas, visceral adipose tissue areas, and index values (p>.05). Table 2 summarizes the statistical results.

4. DISCUSSION

To the best of our knowledge, no previous studies have examined the relationship between antibody levels following SARS-CoV-2 vaccination and body fat distribution. Central obesity was quantified by measuring abdominal circumference instead of BMI in a study examined the relationship between antibody titers and central obesity in individuals who received an mRNA vaccine, and antibody titers developed after the mRNA vaccine were found to be lower in central obesity patients (17). In their meta-analysis on obesity and vaccine immunization, Painter et al. stated that obese people tend to develop poor response to vaccination (18). It is generally accepted that TNF-alpha, IL-6, leptin, and resistin, produced by adipocytes and macrophages in fatty tissue, play a role in poor immunization values in obese individuals (19–21). Studies on obesity have shown that body fat tissue has different functions on different locations. It is stated that visceral adipose tissue is more cellular vascular and contains more inflammatory cells than subcutaneous adipose tissue. In addition, the adipocytes contained in the visceral adipose tissue are metabolically more active than those found in the subcutaneous adipose tissue, and they show more insulin resistance (6).

Given the known relationship between visceral adipose tissue and inflammation, we hypothesized that there might be a relationship between antibody titers and measures of subcutaneous and visceral adipose tissue. However, our results did not support this hypothesis. Although we did not observe a statistically significant relationship between antibody titers and measures of subcutaneous and visceral adipose tissue, our study demonstrated that MRI can be used to accurately measure subcutaneous and visceral adipose tissue.

After the widespread use of SARS-CoV-2 vaccines, people's response rates to vaccines are being investigated by the scientific world, which also causes public debate. Many factors can affect the antibody responses of vaccinated individuals. Among the factors, we investigated whether

obesity, which has effects on a large part of the population and immunization, affects the antibody response in vaccinated individuals.

CT images were started to use for evaluating body fat distribution since the obesity has been recognized as a heterogeneous disease. CT has a more widespread use than MRI, and provides much faster image acquisition. Adipose tissue related measurements can be made with standardized density values due to CT physics. These factors have made CT the first-choice method in this regard. However, the development of automated software and the availability of short acquisition times, standardized measurements of adipose tissue can now be obtained from MRI images as well. To our knowledge, there are very few publications on adipose tissue quantification over MR images with automated software. In a study in 2018, a review was done for the limited number of automated programs that perform fat and muscle tissue analysis from MR images, and the paper stated that many of these methods are not accessible to researchers (10). As stated in the same study, only FATCALC, AMRA® Researcher, and SliceOmatic software are accessible and usable for researchers (10,16,22–24). This study used the FATCALC algorithm, implemented in the NIH's ImageJ application, to quantify abdominal adipose tissue from Dixon MR images (15,16). Compared to manual techniques, the measurement of fat tissue on MR images with automated software has become more standardized, more comparable, and easier to obtain. With the advantages of better soft-tissue resolution provided by MRI and the absence of ionization radiation, furthermore, the opportunity of getting images as fast as CT screening as shown in this article, it can be predicted that the MRI sequences will be used more broadly for quantification of adipose tissue. Moreover, the broad usage of deep learning and artificial intelligence technologies is increasing the requirement for making these measurements by automated software.

This study has limitations. One limitation of this study is that it was conducted on a small sample of healthy healthcare workers with relatively narrow ranges of BMI and body fat distribution. Of the 60 people included in the study, 25 had a BMI of 25 and above, and only 7 had a BMI of 30 and above (obese according to the WHO classification). In addition, the number of volunteers remained low due to the general contraindications and claustrophobic nature of the MR device.

5. CONCLUSION

This study investigates the relationship between SARS-CoV-2 vaccine-induced antibody levels and measures of subcutaneous and visceral adipose tissue using a novel MRI-based method that involves the use of automated software to calculate body fat tissue distributions. This study found no statistically significant relationship between antibody levels and adipose tissue distribution. However, findings demonstrate the feasibility of using MRI and automation algorithms to obtain these measurements. Future research with larger, more diverse samples including individuals with a range of BMIs and body fat distributions could provide more comprehensive insights into this relationship. These insights may have important implications for the design of vaccination strategies that are tailored to specific populations.

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