RESEARCH ARTICLE

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Assessment of Carotid Intima-media Thickness in COVID-19 Survivors

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Abstract

Background and Aim: Coronavirus disease-2019 (COVID-19) infection is associated with cardiovascular diseases in the acute and chronic stages. One of the most common causes of death worldwide is atherosclerosis. Carotid intima media thickness is a method used in the early diagnosis and follow-up of atherosclerosis. This study describes endothelial dysfunction and the risk for pre-atherosclerosis using carotid intima-media thickness (CIMT) measurements in patients with a history of COVID-19 infection.

Materials and Methods: This was a prospective case-control study of 121 patients with 121 COVID-19 infections and 40 healthy controls. Groups were compared according to demographic characteristics, body mass index (BMI), and carotid intima-media thickness. Data obtained were analyzed using SPSS version 22.0.

Results: There was no statistically significant difference between the groups in terms of age, gender, BMI, and blood pressure values. The CIMT value of the group with COVID-19 infection was significantly higher than the control group ($P = 0.003$).

Conclusion: The findings of this study show that CIMT, which is an indicator of early atherosclerosis, was increased in patients with COVID-19.

Keywords: Atherosclerosis, carotid intima-media thickness, COVID-19

INTRODUCTION

Coronavirus disease-2019 (COVID-19) is closely related to a wide spectrum of heart diseases ranging from acute coronary syndrome to heart failure in the acute period and at long-term. The pathophysiological processes underlying COVID-19 are related to systemic inflammatory response, which may develop during the course of any viral infection and support platelet activation, endothelial dysfunction and prothrombotic environment.[1] In particular, severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) virus triggers a native immune response while it has the capacity to recruit non-immune peripheral cells to the infection site by copying itself within the airway epithelium. Thus, COVID-19 may progress with hyper-inflammation due to the massive immune reaction.[2] Atherosclerosis is the most common cause of death worldwide and leads to severe morbidity. Inflammation is central to the development of atherosclerosis. Endothelial dysfunction and disruption of intima-media layer are known as early signs of atherosclerosis. Carotid intima-media thickness (CIMT) is a simple, readily available, non-invasive method allowing objective assessment, which is used in the diagnosis and follow-up of atherosclerotic disorders at the subclinical period.[3-5] Clinical trials have found that CIMT is an important marker for subclinical atherosclerosis.

In this study, we evaluated the relationship between CIMT and the risk of endothelial dysfunction and pre-atherosclerosis in patients with a history of COVID-19 infection.

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MATERIALS AND METHODS

The study included patients who presented to the Cardiology Outpatient Clinic of Kayseri City Hospital between 01.10.2021 and 01.02.2022 dates and had a history of confirmed COVID-19 by laboratory data. Patients who have passed at least 3 months after COVID-19 infection were included. COVID-19 survivor groups were selected from those that demonstrated have COVID-19 by reverse transcriptase-polymerase chain reaction test and computed tomography imaging. Exclusion criteria included smoking, alcohol consumption, obesity, known cardiovascular disease, hyperlipidemia, hypertension, diabetes mellitus, chronic renal failure, thyroid disorder, rheumatic disease, and malignancy. Blood samples and CIMT measurements were obtained from each participant. The CIMT was measured at the supine position with a slight cervical extension. Two measurements were performed on the left and right common carotid arteries (1 cm proximal to bulb) and average value of two measurements were recorded. No measurement was made at areas with visible atheromatous plaque. CIMT was evaluated as the distance between two echogenic lines at the intima-lumen interface and at the media-adventitia interface. The mean CIMT was calculated by dividing the total value of the right and left CIMT. The CIMT measurements were made by a Philips device using B-mode.

The study protocol was approved by the Local Ethics Committee of the Kayseri Training and Research Hospital (approval number: 578, date: 10.02.2022).

Statistical analysis

The categorical variables are expressed as percent while continuous variables are expressed as mean ± standard deviation. The categorical variables were compared using the chi-square test. The normal distribution of continuous variables were tested using Kolmogorov-Smirnov test and histograms. The variables with normal distribution were assessed using Student's t-test, while those with skewed variables were assessed using the Mann-Whitney U test. All statistical analyses were performed using SPSS version 22.0 (Statistical Package for Social Sciences; SPSS Inc., Chicago, IL). A *P* value <0.05 was considered as statistically significant.

RESULTS

The study included 121 patients with a history of confirmed COVID-19 infection (Group 1) and 40 healthy controls (Group 2). The mean age was 31.8 ± 11.3 years in group 1 and 29.7 ± 9.2 years in group 2, indicating no significant difference (*P* = 0.208). Again, no significant difference was observed in gender and body mass index between Group 1 and 2. There was no significant difference in systolic and diastolic blood pressure measurements between Groups 1 and 2. Laboratory findings, including fasting glucose, serum creatinine, C-reactive protein, lipid levels, hemoglobin, and white blood cell count, were similar between the groups [Table 1]. However, it as found that heat rat was significantly higher in group 1 compared to group 1 (*P* = 0.003). In the guidelines, regardless of age and gender, the threshold value for CIMT increase is accepted as >0.9 mm. The CIMT was within the normal range in both groups. However, it was found that CIMT was significantly increased in the COVID-19 group compared to controls (0.57 ± 0.23 mm vs 0.41 ± 0.12 mm; *P* = 0.003) [Table 2].

DISCUSSION

In this study, we found that CIMT, which is considered an early indicator of atherosclerosis, was significantly higher in patients who survived the COVID-19 infection compared with controls. The CIMT as measured by sonography, is considered as an inexpensive, simple, reproducible, and non-invasive marker used to assess the presence and extent of atherosclerosis in the epidemiological, clinical and observational studies. In the autopsy series, a close association was detected between carotid artery and coronary artery atherosclerosis. Coronary angiography provides information about lesions in the lumen; however, the CIMT measurement allows assessment

Table 1: Comparison of the patient and control groups in terms of laboratory parameters

Variables	Control group (*n*=40)	Patients group (*n*=121)	*P*
Fasting glucose (mg/dL)	84±12	90±11	0.23
Creatinine (mg/dL)	0.8±0.3	0.7±0.4	0.53
CRP (mg/L)	2.3±1.1	2.6±1.6	0.61
White blood cells (10^3/µL)	7426±1670.2	7738.4±1673.1	0.19
Hemoglobin (gr/dL)	14.2±1.64	14.5±1.78	0.37
Total cholesterol (mg/dL)	130.4±25.1	135.2±22.2	0.27
LDL cholesterol (mg/dL)	99.7±20.1	95.6±20.1	0.31
HDL cholesterol (mg/dL)	41.14±11.2	40.88±11.6	0.47
Triglycerides (mg/dL)	86.4±62	73.1±26.5	0.35

CRP: C-reactive protein, LDL: Low-density lipoprotein, HDL: High density lipoprotein

Tablo 2: Comparison of patient and control groups in terms of demographic characteristics and other parameters

Variables	Control group (*n*=40)	Patients group (*n*=121)	*P*
Age (year)	29.7±9.2	31.8±11.3	0.208
Male sex, n (%)	16 (40%)	53 (43.8%)	0.712
BMI (kg/m²)	23.2±4.1	24.1±3.7	0.758
Brachial SBP (mmHg)	119±26	108±38	0.505
Brachial DBP (mmHg)	78±10	72±11	0.871
Heart rate (min)	74±8	89±16	0.003
CIMT (mm)	0.41±0.12	0.57±0.23	0.003

BMI: Body mass index, CIMT: Carotid intima-media thickness, DBP: Diastolic blood pressure, SBP: Systolic blood pressure

of atherosclerosis in the early phase where no anatomical stenosis is present and atherosclerosis is limited to the vessel wall. It was shown that each 0.130 mm increase in the carotid artery IMT is associated with a 1.4-fold increase in the risk for myocardial infarction, coronary death, and any coronary event, while each 0.03 mm/year increase in the carotid artery IMT is associated with to a 3.1-fold increase in the risk for coronary event and 2.2-fold increase the risk for myocardial infarction and coronary death.[6]

There is pathophysiological and clinical evidence showing that COVID-19 infection is associated to high cardiovascular risk. Recent studies have proven long-term cardiovascular risks of COVID-19 and increased disease burden.[7-10] The COVID-19 infection can lead to myocardial damage and fibrosis at long-term by ACE2 down-regulation and attenuating the protective and anti-inflammatory role of ACE2.[11] COVID-19 is considered as a systemic disease characterized by an altered immune response, which can lead to mild chronic inflammation after recovery from severe acute inflammation and the acute phase of COVID-19. According to studies, endothelitis and endothelial dysfunction have developed during COVID-19 infection.[12-16] Inflammation, bleeding, thrombosis, altered vascular tone, edema, and increased matrix metalloproteinase levels in the subintimal area can cause functional and structural changes. Thus, phenotypic alterations that may lead to hypertrophy of vascular smooth muscle cells occur through arterial stiffening and oxidative stress developed because of pathological inflammation by cytokine release during COVID-19 infection.[17-19] Recent data showed that severe pulmonary symptoms do not only develop due to respiratory distress syndrome but also due to macro-and micro-vascular endothelial injury and dysfunction. The European Society of Cardiology has recommended clinical assessment of endothelium function during the recovery period in COVID-19 patients to prevent long-term cardiovascular consequences.[20]

In studies using flow-mediated dilatation (FMD) to demonstrate endothelial dysfunction, a remarkable dysfunction was shown even months after disease onset.[21] In support of these studies, we also showed increased CIMT as a marker of endothelial dysfunction. The inflammatory response associated with COVID-19 can cause carotid artery stiffness and changes in CIMT similar to those typically observed following acute bacterial and viral infections. Observational studies with acute infectious agents have demonstrated the potential for significant changes in CIMT and other morphological indices related to infection-related inflammation. It is thought that these mechanisms directing inflammation-related vascular alterations may have potential effects on vascular health, progression of atherosclerosis and risk for cardiovascular events which can be affected by SARS-CoV-2. On the contrary to our results, Szeghy *et al.*,[22] found no change in CIMT by COVID-19 infection in young adults. However, the sample size was smaller than that of our study. Additionally, the authors emphasized that CIMT might be affected in patients with persistent symptoms. In a study by Oikonomou *et al.*,[23] the endothelial function remained significantly lower than controls on months 1 and 6 after admission despite considerable recovery during the follow-up period.[22] In previous studies, the FMD reduction has been linked to the severity of acute disease as a marker of endothelial dysfunction. However, in the study by Riou *et al.*,[24] endothelial dysfunction was more commonly observed in patients with a history of COVID-19 infection regardless from disease severity. In our study, the CIMT, as a marker of endothelial dysfunction, was found to be higher in the COVID-19 group regardless of disease severity. In a study by Ambrosino *et al.*,[25] improvement was detected in endothelial dysfunction in COVID-19 patients who underwent pulmonary rehabilitation. This indicates the importance of early detection of endothelial dysfunction to reduce potential cardiovascular risk in the future.

CONCLUSION

In our study, we showed that the CIMT, a marker for endothelial dysfunction and an early sign of atherosclerosis, was increased in patients with a history of COVID-19 infection. It is clear that the COVID-19 infection leads to more aggressive disease in patients with cardiovascular disease and a wide spectrum of cardiac disorders from acute coronary syndrome to arrhythmias during acute infection. However, it is unclear what can COVID-19 cause

at long-term in healthy individuals. It may be helpful to detect early changes using readily available parameters and define treatment protocols to decrease cardiovascular diseases in the future. There is a need for further studies with a larger sample size and longer follow-up.

Ethics

Ethics Committee Approval: The study protocol was approved by the Local Ethics Committee of the Kayseri Training and Research Hospital (approval number: 578, date: 10.02.2022).

Informed Consent: Prospective case-control study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Y.D., A.T.Ö., Concept: Y.D., A.T.Ö., Design: Y.D., A.T.Ö., Data Collection or Processing: Y.D., A.T.Ö., Analysis or Interpretation: Y.D., A.T.Ö., Literature Search: Y.D., A.T.Ö., Writing: Y.D., A.T.Ö.

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