ISSN: 2405-8181
E-ISSN: 2405-819X

CARDIOVASCULAR ACADEMY SOCIETY

INTERNATIONAL JOURNAL OF THE CARDIOVASCULAR ACADEMY

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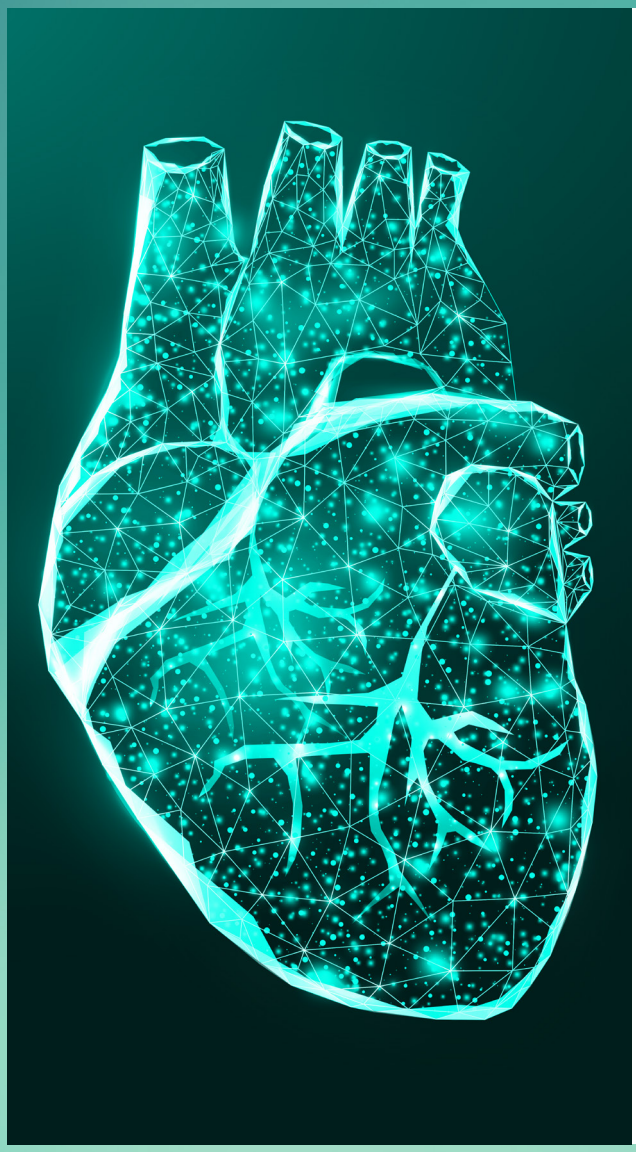
VOLUME: 9 ISSUE: 1 MARCH 2023



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Web: www.galenos.com.tr
Publisher Certificate Number: 14521
Publication Date: April 2023
ISSN: 2405-8181 **E-ISSN:** 2405-819X
International scientific journal published quarterly.

INTERNATIONAL JOURNAL OF THE CARDIOVASCULAR ACADEMY

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INTERNATIONAL JOURNAL OF THE CARDIOVASCULAR ACADEMY
OFFICIAL PUBLICATION OF THE CARDIOVASCULAR ACADEMY SOCIETY

VOLUME: 9
ISSUE: 1
MARCH 2023

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EDITORIAL

DOI: 10.4274/ijca.23022023
Int J Cardiovasc Acad 2023;9(1):1-2

Earthquakes and Cardiovascular Diseases

Mehdi Zoghi

Department of Cardiology, Faculty of Medicine, Ege University, İzmir, Turkey

A catastrophic earthquake could affect the population at all levels. Following an earthquake, as well as human and economic losses, the public health and the rate of cardiovascular diseases (CVDs) can be negatively affected. In the 21st century, there have been more than 20 earthquakes ranging in intensity from 6 to 9.3.[1] After the Christchurch, New Zealand, the 2011 earthquake a significant increase in overall cardiovascular events (P = 0.003), ST elevation myocardial infarctions (P = 0.016) and stress cardiomyopathy admissions have been reported.[2] In the first year, people living in the damaged areas had approximately 10% more cardiovascular hospitalizations.[3]

Previous studies have showed that the prevalence of acute coronary syndrome, hypertension, heart failure and arrhythmias increase in areas after a high-impact earthquake.[4-6] The post-traumatic mental stress is the central reason for increasing the risk of CVDs, especially (25% more) in the older population.[7-9] The onset of acute cardiovascular events following earthquakes has been variable from the first day of the event to weeks and months [Figure 1]. Leor *et al*.[10] have reported that there was an increase in sudden cardiac deaths on the day of the Northridge earthquake 1994, compared with the week before and after the earthquake. The 15 minutes after Noto Peninsula earthquake 2007, in Japan, an acute coronary syndrome and 72 h after the event the first case of stroke was reported by Tsuchida *et al*.[11]

The pathophysiology of earthquake-related cardiovascular events is suggested to be triggered by the activation of the sympathetic nervous system (SNS), Hypothalamic-pituitary-adrenal (HPA) axis, endothelial dysfunction, abnormal circadian rhythms, increased platelet activation, and vascular thrombosis.[12] The activation of the SNS and HPA axis cause releasing of catecholamines, corticotrophin hormone and, cortisol. Stress-induced mechanisms and excess hormones releasing lead to the progression of atherosclerosis, most etiology of the mortality.[13] Stress can also activate the renin-angiotensin system and increase the production of circulating angiotensin II [Figure 2].[14]

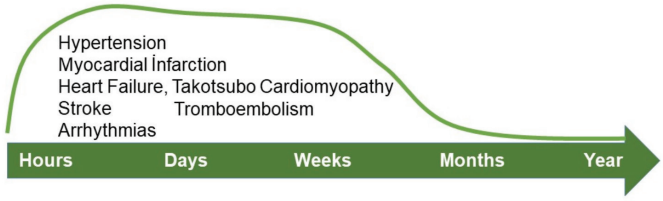

Figure 1: Time period of earthquake-related cardiovascular events

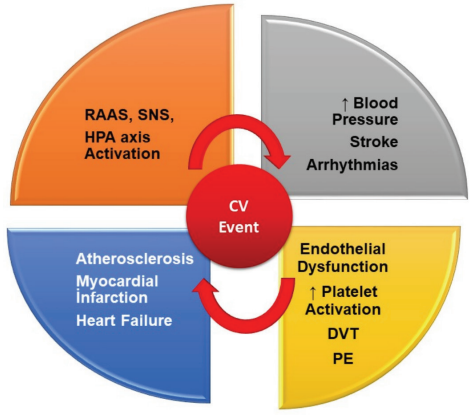

Figure 2: Pathophysiology and cardiovascular effects of an earthquake

To cite this article: Zoghi M. Earthquakes and Cardiovascular Diseases. Int J Cardiovasc Acad 2023;9(1):1-2

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Received: 23.02.2023
Revised: 23.02.2023
Accepted: 23.02.2023
Published Online: 14.04.2023

In conclusion, earthquake-induced CVDs are attributed to the abnormalities in the SNS, HPA axis, and neuroendocrine pathways triggered by mental and physical stresses. The rate and duration of the increases in cardiovascular events depend on the levels of earthquake damage, stress and, socio-economic stability.

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RESEARCH ARTICLE

DOI: 10.4274/ijca.76486
Int J Cardiovasc Acad 2023;9(1):3-8

The Relationship of Body Mass Index with Insulin Resistance, hs-CRP, and Lp(a) Levels in Female Gender

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Abstract

Background and Aim: Chronic obesity causes adipose tissue to produce mediators that promote atherogenesis and vascular inflammation, contributing to hyperlipidemia, diabetes, hypertension, and cardiovascular disease (CVD). This study aimed to examine the relationship between body mass index (BMI) with homeostatic model assessment for insulin resistance (HOMA-IR), high-sensitivity C-reactive protein (hs-CRP), and lipoprotein(a) [Lp(a)] levels in females.

Materials and Methods: One hundred thirty-one females participated in the study: 46 morbidly obese, 38 obese, 25 overweight, and 22 normal BMI. To determine insulin resistance, all participants had their HOMA-IR values assessed. As an inflammatory marker, hs-CRP and as a lipid biomarker, Lp(a) were checked.

Results: A significant difference in the HOMA-IR was found between the normal and the obese ($P = 0.001$) and morbidly obese ($P = 0.0001$) participants. There was also a significant difference in terms of HOMA-IR between the overweight and morbidly obese ($P = 0.001$) groups. In paired-group comparisons, hs-CRP was found to be significantly different between the normal group and obese ($P = 0.001$) and morbidly obese ($P = 0.0001$). Additionally, a significant difference in terms of hs-CRP between the overweight and morbidly obese participants ($P = 0.003$) was found. When Lp(a) values were compared, there was a significant difference between the normal group and those who were overweight ($P = 0.0001$), obese ($P = 0.0001$), and morbidly obese ($P = 0.0001$). A significant positive correlation of BMI was shown with HOMA-IR, hs-CRP, and Lp(a) levels.

Conclusion: Elevated BMI in females is related to insulin resistance, elevated hs-CRP, and Lp(a), which confer a residual risk for CVD.

Keywords: Body mass index, hs-CRP, insulin resistance, lipoprotein(a)

INTRODUCTION

The prevalence of overweight, obesity, and morbid obesity is on the rise in today's society.[1,2] Accumulating evidence backs up the claim that body mass index (BMI) over the normal range is an independent risk factor for a variety of illnesses[3-5] including atherosclerosis. Low grade inflammation related to inflammatory mediators released from adipose tissue is called obesity-related inflammation.[6] Inflammation brought on by obesity increases the risk of a systemic inflammatory response, which may lead to several metabolic dysregulations. It has long drawn attention because atherosclerosis is a chronic inflammatory event and that inflammation has a part in every

To cite this article: Uludağ B, Solmaz H, Alihanoğlu Yİ, Kılıç İD, Enli Y. The Relationship of Body Mass Index with Insulin Resistance, hs-CRP and Lp(a) Levels in Female Gender. Int J Cardiovasc Acad 2023;9(1):3-8

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Received: 07.03.2023
Revised: 07.03.2023
Accepted: 13.03.2023
Published Online: 14.04.2023

stage of the pathogenesis of atherosclerosis. In overweight and obesity, metabolic problems such as reduced peripheral glucose absorption, insulin resistance, and glucotoxicity may ultimately result in increased blood glucose.[7,8] The argument at which a rise in BMI is associated with an increase in overall mortality is, however, constant, although its precise value varies between studies and populations.[9]

Various inflammatory mediators, including interleukin-1 (IL-1), tumor necrosis factor-a (TNF-a), and IL-6, are released by adipocytes and are key players in the liver's production of high-sensitivity C-reactive protein (hs-CRP).[10,11] Several studies have demonstrated that inflammatory biomarkers, such as CRP, might increase risk estimation and the capacity to predict associated illnesses[12], considering the expanding evidence linking inflammation to various chronic health disorders, including diabetes, metabolic syndrome, and CVD.[13] On the other hand, lipoprotein(a) [Lp(a)], a lipid biomarker, is thought to promote atherosclerotic conditions by pro-atherogenic, pro-inflammatory, and/or pro-thrombotic processes, despite a lack of consensus.[14] Furthermore, various prospective studies have demonstrated that higher plasma levels of Lp(a) are a potential risk for stroke and CVD. [15,16]

The relationship between inflammatory markers and BMI appears to have conflicting results among studies.[17,18] Considering all mentioned above, we assessed the relationship between insulin resistance, inflammation, lipid biomarkers, and BMI by the using of measurements of homeostatic model assessment for insulin resistance (HOMA-IR), hs-CRP, and Lp(a) levels.

MATERIALS AND METHODS

Study population

In this cross-sectional study, 131 female participants between the ages of 18 and 65 with 46 morbidly obese, 38 obese, 25 overweight, and 22 normal BMI were included from October 2012 to January 2014. The individuals' age, height, and weight values were noted. The individuals' weight in kilos was determined using a calibrated digital balance. The height was taken in cm using a wall-mounted, transportable measuring tape. By dividing an individual's weight in kilos by their height in meters squared, the BMI is obtained [weight (kg)/height (m^2)]. Those with a BMI of 18.5-24.9 kg/m^2 were categorized as normal, 25-29.9 kg/m^2 as overweight, 30-39.9 kg/m^2 as obese, and ≥40 kg/m^2 as morbidly obese.[19,20]

Blood was taken from the participants after 12 hours of fasting for evaluating blood glucose, hemoglobin, creatinine, lipid parameters, insulin, and HbAIc and was immediately studied. HOMA-IR value was computed using the following equation: (fasting blood glucose x fasting insulin) / 405. [21] Plasma samples were separated and maintained at -80 °C in order to analyze hs-CRP and Lp(a). Before processing, the samples were brought to room temperature. For hs-CRP, a BioCheck kit was used, and for Lp(a), an ASSAYPRO brand kit was employed. Patients with known coronary artery disease, heart failure, valve disease, prosthetic valves, atrial fibrillation/flatter rhythm, known diabetes, and patients with indications for coronary angiography were excluded from the study. Additionally, because they may affect the levels of inflammatory parameters to be assessed, patients with acute infections, asthma, rheumatological conditions, renal failure, pulmonary emboli, a history of cerebrovascular disease, malignancy, and patients who had undergone trauma or surgery was also eliminated from the study.

Kit support was given by the Pamukkale University Scientific Research Projects Unit as part of the Scientific Research Project with the project number 2012TPF033. The study protocol was accepted by the Pamukkale University Non-Interventional Clinical Research Ethics Committee (decision no: 12.06.2012-11). Good Clinical Practices were followed in the design of the study, the Declaration of Helsinki was adhered to, and all individuals gave their written informed permission.

Statistical analysis

SPSS (Statistical Package for the Social Sciences) 20 for Windows was used for the study's statistical analysis. Continuous variables were represented by mean ± standard deviation, median (minimum-maximum values), and categorical variables by numbers (percentage). In independent group comparisons, when parametric test assumptions are provided, analysis of variance and significance test of difference between two means; when parametric test assumptions were not met, Kruskal-Wallis analysis of variance and Mann-Whitney U test are used. Using the chi-square test, differences between qualitative data were analyzed. The Pearson correlation coefficient was used to examine the relationship between variables. $P < 0.05$ was used to determine statistical significance.

RESULTS

Of the female individuals included in the study according to the BMI value, 22 were in the normal group, 25 were in the overweight, 38 were obese, and 46 were in the morbidly obese group. The baseline characteristics of the study groups are shown in Table 1. While the mean age of the females in the normal group was 33.72 ± 7.47 years, this value was 48.20 ± 15.48 years in the overweight group, 48.31 ± 15.83 years in the obese group and 39.69 ± 12.10 years in the morbidly obese group. Age differences between the groups were observed to be statistically significant (p=0.0001). The comparison both HOMA-IR and inflammatory parameters between groups are shown in Table 2. While the HOMA-IR value was 2.08 ± 1.49 in individuals with normal group, it was 2.84 ± 3.00 in the

overweight group, 3.86 ± 2.59 in the obese group, and 3.81 ± 2.60 in the morbidly obese group. HOMA-IR value differences between the groups were observed to be statistically significant ($P = 0.0001$). In paired group analysis, a significant difference in terms of HOMA-IR was observed in the normal group and the obese ($P = 0.001$) and morbidly obese ($P = 0.0001$) groups. Additionally, HOMA-IR value was observed to be significantly different between the overweight and morbidly obese ($P = 0.001$) groups. The mean hs-CRP value was 0.07 ± 0.05 mg/L in participants with normal BMI, 0.87 ± 1.36 mg/L in the overweight group, 1.44 ± 1.30 mg/L in the obese group, and 2.12 ± 1.22 mg/L in the morbidly obese group. Hs-CRP value differences between the groups were observed to be statistically significant ($P = 0.0001$). In paired-group comparisons, it was found that there were significant differences in hs-CRP levels between the normal BMI group and obese ($P = 0.001$) and morbidly obese ($P = 0.0001$) groups. Additionally, a significant difference in hs-CRP levels between the overweight and morbidly obese groups was observed ($P = 0.003$). The mean Lp(a) value of females included in the normal group was 26.67 ± 4.73 mg/dL, for overweight it was 53.25 ± 12.78 mg/dL, for obese, it was 55.72 ± 6.09 mg/dL, and for morbid obese it was 56.13 ± 7.12 mg/dL. Lp(a) value differences between the groups were observed to be statistically significant ($P = 0.0001$). In paired-group comparisons, a significant difference was found between the normal group and the overweight ($P = 0.0001$), obese ($P = 0.0001$) and morbidly obese ($P = 0.0001$) groups. There were also significant positive correlations of BMI with HOMA-IR, hs-CRP, and Lp(a) ($P = 0.0001$, $r = 0.288$ vs $P = 0.0001$, $r = 0.480$ vs $P = 0.0001$, $r = 0.528$), respectively [Table 3].

DISCUSSION

In addition to the treatment of conventional risk factors that induce ischemia processes, primary preventive approaches are crucial for controlling the epidemic growth of cardiovascular illnesses. To obtain a true risk estimation and the individuals who would benefit from therapy, it is necessary to identify all possible risk variables. In our study, we observed that insulin resistance, was measured by HOMA-IR, increased among

Table 1: Baseline characteristics of the study population

	Normal (*n*=22)	Overweight (*n*=25)	Obese (*n*=38)	Morbidly obese (*n*=46)	*p*-value
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	
Age	33.72±7.47	48.20±15.48	48.31±15.83	39.69±12.10	0.0001*
Weight, kg	57.89±8.98	70.56±6.74	88.63±10.42	121.53±17.74	0.0001*
Height, cm	163.09±7.34	159.40±6.17	159.78±6.32	161.84±7.29	0.292
BMI, kg/m^2	21.59±2.06	27.59±1.31	34.60±2.88	46.24±6.29	0.0001*
Glucose, mg/dL	89.21±12.52	94.23±10.29	96.52±11.44	98.14±12.56	0.115
Insulin, µIU/mL	9.07±5.62	11.33±9.55	15.38±9.43	15.50±10.52	0.0001*
Hb, g/dL	12.87±0.79	13.49±1.14	13.16±1.17	12.99±1.11	0.205
Cre, mg/dL	0.60±0.06	0.69±0.08	0.66±0.09	0.62±0.09	0.003*
T.chol, mg/dL	172.40±33.7	193.72±41.58	192.50±29.84	192.26±26.59	0.018*
TG, mg/dL	76.50±32.30	131.64±65.53	151.23±72.11	143.04±69.35	0.0001*
LDL-C, mg/dL	95.09±27.52	112.68±41.71	117.78±24.45	115.28±26.49	0.005*
HDL-C, mg/dL	62.00±11.32	54.68±14.14	47.18±11.38	48.30±8.40	0.0001*

BMI: Body mass index, Cre: Creatinine, Hb: Hemoglobine, HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, SD: Standard deviation, T.chol: Total cholesterol, TG: Triglyceride, *Statistically significant

Table 2: Comparison of HOMA-IR, hs-CRP, and Lp(a) between groups

	Normal (*n*=22)	Overweight (*n*=25)	Obese (*n*=38)	Morbidly obese (*n*=46)				
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	p†	p‡	p§	p‖
HOMA-IR	2.08±1.49	2.84±3.00	3.86±2.59	3.81±2.60	NS	**0.001***	**0.0001***	0.012*
hs-CRP	0.07±0.05	0.87±1.36	1.44±1.30	2.12±1.22	NS	**0.0001***	**0.0001***	0.0001*
Lp(a)	26.67±4.73	53.25±12.78	55.72±6.09	56.13±7.12	**0.0001***	**0.0001***	**0.0001***	NS

P†: P-value comparing normal and overweight individuals, p‡: P-value comparing normal and obese individuals, p§: P-value comparing normal and morbidly obese individuals, p‖: P-value comparing overweight and morbidly obese individuals, BMI: Body mass index, HOMA-IR: Homeostatic model assessment of insulin resistance, hs-CRP: High-sensitivity C-reactive protein, Lp(a): Lipoprotein(a), SD: Standard deviation, *Statistically significant

Table 3: Correlation of BMI with HOMA-IR, hs-CRP, and Lp(a)

	r	*p*-value
HOMA-IR	0.288	0.0001*
hs-CRP	0.480	0.0001*
Lp(a)	0.528	0.0001*

BMI: Body mass index, HOMA-IR: Homeostatic model assessment of insulin resistance, hs-CRP: High-sensitivity C-reactive protein, Lp(a): Lipoprotein(a), *Statistically significant

females with BMI over the normal range, and that inflammatory and lipid biomarkers such as hs-CRP and Lp(a) rose in tandem with the increase in BMI.

Revealing the association between BMI and HOMA-IR, may contribute to the implementation of strategies, dietary and lifestyle modifications that are required for the prevention or reduction of the onset of type 2 diabetes (T2DM), which is among the most important health concerns of today.[22] According to the our study results, we found that HOMA-IR rise progressively with increasing BMI, and in paired-group comparisons, the average HOMA-IR value of the control group was significantly lower compared to the obese and morbidly obese groups. Additionally, there was a significant difference in HOMA-IR between the overweight and morbidly obese females. The results of our study were in agreement with those of previous studies[23,24], the HOMA-IR values used to assess insulin resistance exhibited a linear association with BMI. In addition, consistent with our study results, two recent cross-sectional studies revealed that individuals with abnormal HOMA-IR values had significantly higher BMI. [25,26] Furthermore, in a study by Singh *et al*. [27], it was revealed that a HOMA-IR threshold of 2.5 was shown to be sufficient for the diagnosis of metabolic syndrome in terms of sensitivity and specificity. In our study, the HOMA-IR value in the overweight, obese, and morbidly obese groups were shown to be greater than this value. Therefore, managing body weight may be crucial in clinical practice, not just for obese and morbidly obese females but also for overweight females.

In this study, an important marker for assessing the risk of CVD, hs-CRP levels, was observed to rise with an increase in BMI. This might be the result of excessive adipose tissue, which causes systemic inflammation. [28,29] In a study by Kawamoto *et al*. [30], BMI was shown to be independently and significantly related to hs-CRP in participants aged <74 years. Similarly, Weinbrenner *et al*. [31] showed that elevated hs-CRP concentrations were related to increased abdominal fat. Additionally, our study's findings are supported by previous research that shows diet-induced weight reduction is related to reduced blood concentrations of IL-6, TNF alpha, and CRP. [32] Similar outcomes were seen in those who received gastric bypass surgery. [33-35] Our findings support the view that obesity is responsible for a low degree of systemic inflammation.

According to the findings of our study, Lp(a), a lipid biomarker known to carry residual risk and related to early accelerated atherosclerosis, ischemic CVD, and calcific aortic stenosis[36-38], increased concurrently with the rise in BMI. Similar to our study results, Bostan *et al*.[39] revealed that the Lp(a) levels were significantly higher in obese individuals than in overweight individuals. This is in accordance with the results of a previous study by Aaseth *et al*.[40], which showed that Lp(a) levels considerably decreased in obese individuals who underwent gastric bypass surgery. Additionally, Teng *et al*.[41] demonstrated that important risk variables for AMI include BMI and Lp(a) levels. In the instance of initial AMI, they observed an important additive interaction of Lp(a) and BMI, indicating that Lp(a) raises one's risk of initial AMI when BMI is high.

On the other hand, several studies have focused on the association of low Lp(a) levels and the higher risk of incident T2DM. A recent meta-analysis indicated that Lp(a) thresholds of 3 to 5 mg/dL are associated with a 38% increased risk of T2DM than thresholds of >27 to 55 mg/dL.[42] In contrast, Wang *et al*.[43] observed that Lp(a) values in individuals with diabetes in the Chinese population were significantly higher than in non-diabetic individuals. In another recent study, it was found that elevated Lp(a) levels of >28.72 mg/dL may reduce T2DM risk, but only in males and those aged above 60 years.[44] In our study, although all groups had Lp(a) levels that above those considered extremely low Lp(a) threshold values (e.g. <5 mg/dL), prospective studies must gain a deeper understanding and clarify the causal relationship in this topic.

Study limitations

We realize that our study has several limitations. Our study's sample size was quite small. We used a cross-sectional design, therefore, we were unable to gain predictive and prognostic information by following the patients. To verify our findings, we need a multicenter study with a greater number of participants and a prospective design. The incompatibility in terms of age between the control and patient groups seems to be another limitation of our study. In addition to being a risk factor for CVD, age is associated with an increased likelihood of additional cardiac risk factors. To reduce these effects of age, we excluded individuals with traditional risk factors from our study Additionally, since most types of CVD are more prevalent in older adults than in the general

population, we selected patients under the age of 65, which is defined as "young" by the World Health Organization. Moreover, the current studies do not indicate a relationship between HOMA-IR and age.[45] On the other hand, Lp(a) is frequently measured just once, on the assumption that it does not alter with age.[46] Of note, the results of studies on the relationship between age and hs-CRP are inconsistent.[47] Most studies comparing serum levels of hs-CRP and showing the reported rise in hs-CRP levels with increasing age, included elderly patients or compared participants aged ≥65 to <65 years.[48,49]

CONCLUSION

Given the direct relationship of HOMA-IR, hs-CRP, and Lp(a) levels with elevated levels of BMI, the assessment of these indices may pave the way for the implementation of measures that contribute to the diagnosis, management, and the course of CVDs and associated risk factors in female individuals.

Ethics

Ethics Committee Approval: The study protocol was accepted by the Pamukkale University Non-Interventional Clinical Research Ethics Committee (decision no: 12.06.2012-11).

Informed Consent: All individuals gave their written informed permission.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: B.U., Y.İ.A., Concept: B.U., Y.İ.A., Design: B.U., Y.İ.A., İ.D.K., Data Collection and/or Processing: B.U., Y.İ.A., İ.D.K., Y.E., Analysis and/or Interpretation: B.U., Y.İ.A., Literature Search: H.S., Writing: B.U., H.S.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: Kit support was given by the Pamukkale University Scientific Research Projects Unit as part of the Scientific Research Project with the project number 2012TPF033.

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RESEARCH ARTICLE

DOI: 10.4274/ijca.14633
Int J Cardiovasc Acad 2023;9(1):9-15

The role of Speckle Tracking Echocardiography and Three-dimensional Echocardiography in the Assessment of Left Ventricular Systolic Function in Type II Patients with diabetes with Negative Myocardial Perfusion Imaging in Correlation to Multi-gated Acquisition Scan

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Abstract

Background and Aim: Two-dimensional (2D) speckle tracking echocardiography (STE) has shown promising results being a recent technology to assess "myocardial performance" in cardiac patients. Three-dimensional echocardiography 3DE has been shown to be accurate in the assessment of left ventricular (LV) systolic function. The multigated acquisition (MUGA) scan provides a more accurate quantification of the ventricular ejection fraction To Assess the role of 2D-STE and 3DE in the assessment of LV systolic function in type II patients with diabetes with negative myocardial perfusion imaging in correlation with the MUGA scan.

Materials and Methods: The study included 30 patients with type 2 diabetes mellitus (T2DM) [Group 1, 25 (83%) female and 5 (16%) males with mean age 48.40 ± 7.44], their stress myocardial perfusion imaging was negative for coronary ischemia. The control group included 15 apparently healthy age and sex-matched subjects, [Group 2, 11 (73%) females and 4 (26%) males with mean age 50.20 ± 7.74], LV systolic function was evaluated using conventional, TDI, 2D-STE (LV-GLS), 3-DE and MUGA scan.

Results: The group with diabetes showed statistically highly significant reduction in LV-GLS (-18.07 ± 2.73 in group 1 vs -21.24 ± 1.29 in group 2, $P < 0.001$), and in 3D LVEF (52.30 ± 5.28 in Group 1 vs 58.93 ± 4.69 in Group 2, $P < 0.001$). We found an agreement between three modalities (speckle tracking, 3DE and MUGA scan) by 33% in 10 patients [3 patients (10%) had impaired LV functions and 7 patients (23%) had preserved LV functions]. There was an agreement between speckle tracking and 3D echo by 76.6% in 23 patients [16 patients (53.3%) had impaired LV functions and 7 patients (23.3%) had preserved LV functions].

Conclusion: T2DM is associated with subclinical LV systolic dysfunction that can be assessed by different noninvasive modalities (speckle tracking, 3DE and the MUGA scan). 2D speckle tracking and 3DE might have an edge compared with MUGA scan in the detection of subclinical LV systolic dysfunction.

Keywords: DM, 2D-STE, 3D Echo, MPI, MUGA scan

To cite this article: Ahmed T, Naiem M, Said T, Zahran M. The role of Speckle Tracking Echocardiography and Three-dimensional Echocardiography in the Assessment of Left Ventricular Systolic Function in Type II Patients with diabetes with Negative Myocardial Perfusion Imaging in Correlation to Multi-gated Acquisition Scan. Int J Cardiovasc Acad 2023;9(1):9-15

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Received: 26.09.2022
Revised: 23.03.2023
Accepted: 27.03.2023
Published Online: 14.04.2023

INTRODUCTION

Early detection and proper treatment of diabetic heart disease are important because focusing on early lifestyle interventions and proper updated guideline - directed medical therapy could prevent or delay the complications including heart failure, with the drawbacks and burdens to the national healthcare systems.

Two-dimensional (2D) speckle tracking echocardiography (STE) has the advantage of being accurate, reproducible, and angle independent, and it enables a complete assessment of regional and global cardiac function.

2D STE has shown promising results being a recent technology to assess "myocardial performance" in cardiac patients.[1]

Real time 3DE has the advantages of being a relatively low cost, available, and offering the option of live 3D imaging acquisition. It has shown a particular edge by being more accurate for the assessment of LV-volumes and functions.[2]

Myocardial perfusion imaging (MPI) single photon emission computed tomography has been found to be a very helpful diagnostic and prognostic tool for the evaluation of subtle LV systolic dysfunction in asymptomatic patients with diabetes without known coronary artery disease.[3]

The MUGA scan was first introduced in the early 1970s and since then has been one of the standard methods for measurement of the left ventricular ejection fraction (LVEF).[4]

Aim of the work

This research aimed to assessing the role of 2D-STE and three -dimensional 3DE in the assessment of LV systolic function in type 2 patients with diabetes with negative myocardial perfusion imaging for coronary ischemia in correlation to MUGA scan.

Patients

This study was conducted on 30 patients with type 2 diabetes presented to the cardiology clinic presenting with chest pain or dyspnea with negative stress myocardial perfusion imaging (MPI) for ischemic coronary artery disease (Group 1).

The control group (Group 2) included 15 healthy subjects, they were aged and sex matched.

Group 1 was further sub-classified in to 3 subgroups (A, B & C) according to their MUGA LVEF, LV-GLS, and 3D LVEF respectively.

All patients included in the study accepted oral and written consent, and the study was approved by the Ethical Committee of Al-Azhar University Faculty of Medicine for Girls, approval number 202209/543 (date: 28.09.2022).

Patients with documented ischemic heart disease, valvular heart disease or congenital heart disease, hypertension, arrhythmias, chronic pulmonary disease, and patients with associated co-morbidity were excluded from the study.

MATERIALS AND METHODS

All patients included in this study were subjected to through history taking and clinical examination.

Echocardiography

All patients underwent conventional transthoracic echocardiography in both the supine and left lateral positions using the Vivid-9GE system. All cases were examined using multifrequency (2.5-3.5 MHz) matrix probe M3S with simultaneous ECG recording. For image acquisition, three cardiac cycles were recorded in each view with the patient holding breath.

All images were digitally stored for off-line analysis.

The following data were obtained:

a- Using 2D and 2D guided M-mode to assess: LV end-systolic and end-diastolic volumes (mL^3), LVEF (%), fractional shortening (%), interventricular septum end-diastolic diameter (mm), and LV posterior wall end-diastolic diameter (mm).

b- Using convention Doppler echo to assess: mitral E and A wave Velocities (cm/s), E/A ratio.

c- Using tissue Doppler imaging to assess: S velocity, E' velocity, A' Velocity, and E/E' ratio.

Two-dimensional speckle tracking

Speckle tracking analysis for the left ventricle was recorded in apical 4, 2, and 3 chambers. The LV longitudinal strain was measured using 2D speckle tracking analysis with QRS onset as the reference point. During analysis, the endocardial border was manually traced at end systole and the region of interest width was adjusted to include the entire myocardium, The LV deformation parameters in each of 18 segments were assessed. Then the global strain was calculated by averaging the strain of all segments.

Real time 3-dimensional echocardiography

RT3DE imaging was performed from the apical window with the patient in the left lateral decubitus position. The data sets were acquired using the wide-angled mode to include the entire LV cavity within the scan volume, where in 4 wedge-shaped sub-volumes were acquired during a single breath-hold. The technique for the acquisition of each sub-volume was triggered by the ECG R wave of every other heartbeat (total of 6 heart

beats) to allow sufficient time for each sub-volume to be stored. Six automatically selected long-axis planes rotated around the long axis of the left ventricle at 30° steps were subsequently used to analyze LV function. LV end diastolic volume (LVEDV), LV end systolic volume (LVESV), and LVEF (EF %) were quantified accordingly.[5]

MUGA scan

Radionuclide angiography was performed using a Philips Cardio-MD system by labeling autologous erythrocytes, performed by injecting the patients with 1.5 mg stannous pyrophosphate. After twenty minutes, thirty MCi technetium-99m pertechnetate was injected. Ten minutes later, imaging acquisition was performed in the left anterior oblique (30° to 40°) view with a digital Gamma camera with the collimator positioned at a caudal angulation of 30°. Processing of the data was followed using standard software and background correction. The LVEF was calculated by digital or manual tracing of the LV end-diastolic and end-systolic images. Planar ECG - gated images of the left ventricle were obtained over multiple cardiac cycles. Each cardiac cycle was then separated into a predetermined number of intervals (16 or 32), according to the number of frames (images) per cardiac cycle. The frame with the highest count represented the end-diastole, and the frame with the lowest count represented the end-systole.[6]

LVEF was then calculated from the equation: net counts in the end-diastolic frame - net counts in the end systolic frame divided by net counts in end-diastole. Net counts are determined by subtracting counts from the background region of interest (next to the left ventricle) from measured LV counts.[6]

This was followed by calculation of the left ventricular end diastolic volume (LVEDV), left ventricular end systolic volume (LVESV), and LVEF.[6]

Statistical analysis

The numerical variable was expressed as mean and standard deviation, independent t-test was used for testing statistically significant differences between the means of the two groups. Pearson's correlation test and correlation coefficient (r) were used to test a positive or negative relationship between two variables. P-value less than 0.05 was considered statistically significant and ≤0.001 highly significant.

RESULTS

The study included (30) patients, (25) females and (5) males with mean age of (48.40 ± 7.44 y) and the control group included 15 healthy individuals (11 female and 4 male) with mean age (50.20 ± 7.74).

As regard the different echo modalities (conventional, 2D strain & 3D Echo) and MUGA parameters: There were a statistically significantly lower values of LV-GLS and 3D-EF in the patient group and higher values of 3D LV ESV and 3D LV EDV in the same group compared with the control group, and a non-significant difference between the two groups as regard the following parameters (2D-EF, 2D LVESV, 2D LVEDV, IVSD, PWD, MUGA-EF, MUGA LV ESV and MUGA EDV), as shown in Table 1.

Left ventricular systolic function in the patients' group

We assessed the LV systolic function of all 30 patients with diabetes by the different echo modalities (conventional, 2D strain & 3D Echo) and by MUGA scan.

We found that 23 patients (76.67%) with impaired LV-GLS (5 of them had impaired LV EF measured by MUGA and 16 patients had impaired LVEF by 3D Echo), 17 patients (56.67%) with impaired LVEF by 3D Echo (3 of them had impaired LV EF measured by MUGA and 16 patients had impaired LV-GLS), 5 patients (16.67%) with impaired MUGA LVEF all of them had impaired LV-GLS, and 3 patients had impaired LVEF by 3D Echo.

There was an agreement between three techniques (2D strain, 3D Echo and MUGA scan) by 33% in 10 patients [3 patients (10%) with impaired function and 7 patients (23%) with preserved function]. Also there was an agreement between the two techniques (2D speckle tracking, 3D echo) by 76.6% in 23 patients [16 patients (53.3%) with impaired function and 7 patients (23.3%) with preserved function], as shown in Figure 1.

We divided the group with diabetes into three groups (A, B, C) according to their MUGA LVEF, LV-GLS, and 3D LVEF, respectively.

Table 1: Comparison between the different echo modalities (conventional, 2D strain & 3D Echo) and MUGA parameters in the patient and the control groups

Variable	Patient	Control	*P*
2D-EF	70.77±7.9	70.27±4.89	0.796
2D LVESV	28.03±3.9	28.6±2.6	0.569
2D LVEDV	47.40±3.96	45±6.09	0.118
IVSD	9.50±1	9.13±.743	0.176
PWD	9.13±1.1	9.60±2.67	0.410
LV-GLS	-18.07±2.73	-21.24±1.29	<0.001
3D-EF	52.30±5.28	58.93±4.69	<0.001
3D LV EDV	67.73±13.32	60.13±11.079	0.051
3D LV ESV	31.87±6.11	25.53±7.15	0.003
MUGA EF	65.50±9.164	67.07±5.66	0.485
LV MUGA EDV	113.20±54.74	92.73±17.64	0.07
LV MUGA ESV	40.83±22.91	37.27±9.13	0.462

A) Comparison between the diabetic subgroups as regard MUGA LVEF

We divided the group with diabetes into two groups according to their LV EF measured by MUGA:

Group 1A: Included 5 patients (4 females and 1 male) with impaired MUGA LVEF <50% (50.2% ± 4.44%).

Group 2A: Included 25 patients (21 females and 4 males) with preserved MUGA LVEF ≥50% (68.56% ± 6.3%).

Patients with impaired LV function by MUGA (group 1): All patients with impaired MUGA LV EF had preserved function by conventional echo and impaired LV GLS, but only 3 patients (60%) had impaired systolic function by 3D Echo, as shown in Table 2.

Patients with preserved LV EF by MUGA (Group 2): (LV EF =67.44% ± 5.7%), were found to be with the following parameters: LV GLS (-17.27 ± 1.9) LV 3DEF (51.2% ± 5.9%)

Comparing the two groups (1A & 2A) as regard the different echo modalities (conventional, 2D strain & 3D Echo) and MUGA parameters: There were a statistically significant higher values of IVSD, MUGA LV ESV and EDV in group 1A and lower value of LV-GLS in the same group compared to the group 2A ($P < 0.05$) and a non-significant difference between the two groups as regard the following parameters (2D-EF, LVESV, LVEDV, PWD, 3D EF, 3D LV ESV and EDV), as shown in Table 3.

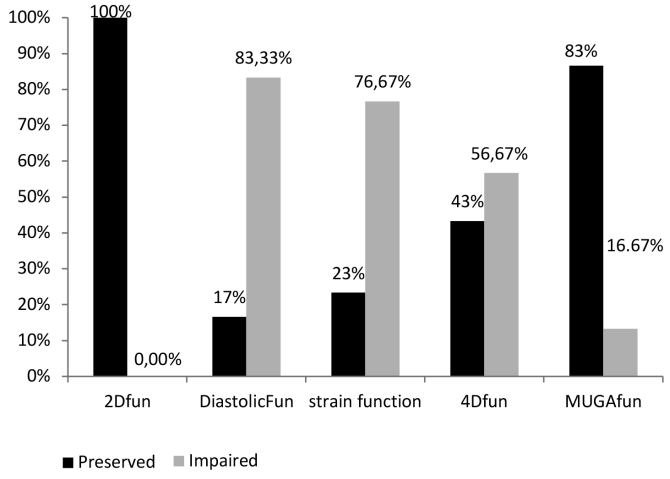

Figure 1: LV function in the study group by different modalities

Table 2: Showing the relationship between group 1A and group 2A regarding other different parameters

Variable		MUGA LV EF		*P*
		Impaired	Preserved	
LV GLS	Impaired	5	18	0.177
	Preserved	0	7	
LV 3D EF	Impaired	3	14	0.869
	Preserved	2	11	

Correlation between MUGA LV EF and different parameters: There was a positive correlation between the MUGA LVEF and LV-GLS at the value of (r=0.511, P = 0.004), a positive correlation with 3D LVEF at the value of (r=0.395, P = 0.031) and a negative correlation with HbA1c value of (r= 0.384, P = 0.036), as shown in Table 4.

B) Comparison between the diabetic subgroups as regard LV-GLS

We divided the group with diabetes as regard LV-GLS into: group 1B: Included 23 patients (18 females and 5 male) with impaired LV-GLS <-20 (-16.94±1.9).

Group 2B: Included 7 patients (all are females) with preserved LV-GLS function >-20 (-21.78±1.9)

Patients with impaired LV function by LV-GLS: All patients with impaired LV-GLS had preserved function by conventional echo, but only (5 patients) with impaired MUGA LVEF and (16 patients) had impaired systolic function by 3D Echo, as shown in Table 4.

There was a statistically significant relationship between both groups in 3D LVEF with (p<0.05).

Correlations between the LV-GLS and different parameters

There was a positive correlation between the LV-GLS and MUGA LVEF at value of (r=0.511, P = 0.004) and a negative correlation with MUGA LVESV at value of (r=0.491, P = 0.006) and MUGA LVESV at value of (r=0.456, P = 0.011), as shown in Table 5.

Table 3: Showing the comparison between group 1A and group 2A regarding the different echo modalities (conventional, 2D strain & 3D Echo) and MUGA parameters

Variable	Group 1A	Group 2A	*P*
2D-EF	68.00±3.32	71.32±8.51	0.16
2D LVESV	28.20±1.79	28.00±4.23	0.866
2D LVEDV	45.60±4.33	47.76±3.87	0.273
IVSD	10.20±.45	9.36±1.03	0.01
PWD	9.00±.71	9.16±1.18	0.694
LVGLS	-15.78±1.47	-18.53±2.71	0.009
EF3D	52.32±5.55	52.20±4.15	0.957
3D LV EDV	66.60±18.02	67.96±12.64	0.839
3D LV ESV	32.00±10.42	31.84±5.19	0.958
LVMUGA EDV	166.80±83.23	102.48±41.81	0.014
LV MUGA ESV	79.00±30.6	33.20±10.67	<0.001

C) Comparison between the diabetic subgroups as regard to LV-3DEF

Patients were classified into two groups according to their LV 3DEF: Group 1C: Included 17 patients (15 females and 2 male) with impaired function <54% (49.76 ± 5.5).

Group 2C: Included 13 patients (10 females and 3 males) with preserved function ≥54 (55.61 ± 2.4).

Patients with impaired LV function by 3D Echo

All patients with impaired LV-3DEF had preserved function by conventional echo, but only (3 patients) with impaired MUGA LVEF and (16 patients) had impaired LV-GLS, as shown in Table 6. There was a statistically significant relation between both groups in LV-GLS with ($P < 0.05$)

Table 4: Showing the correlation between the MUGA LVEF and 3D-EF, LV-GLS and HgbA1C

Variables		Person correlation	Significance
MUGA LVEF	3D-EF	0.395*	0.031
	LV-GLS	0.511*	0.004
	HbA1c	-0.384**	0.036

*Positive correlation, **Nagative correlation

Table 5: Showing the correlation between the LV-GLS and MUGA-LVEF, MUGA-LVEDV and MUGA-LVESD

Variables		Person correlation	Significance
LV-GLS	MUGA-LVEF	0.511*	0.004
	MUGA-LVEDV	-0.456**	0.011
	MUGA-LVESD	-0.491**	0.006

*Positive correlation, **Nagative correlation, MUGA: Multigated acquisition

Table 6: Showing the relationship between group 1C and group 2C regarding other different parameters

Variable		LV-3DEF		*P*
		Impaired	Preserved	
LV-GLS	Impaired	16	7	0.01
	Preserved	1	6	
MUGA LVEF	Impaired	3	2	0.869
	Preserved	14	11	

MUGA: Multigated acquisition, LVEF: Left ventricular ejection fraction

Table 7: Showing correlations between the 3D-LVEF and different parameters

Variables	Person correlation		Significance
3D-LVEF	MUGA LVEF	0.395*	0.031
	LDL	-0.378*	0.039

LDL: MUGA: Multigated acquisition, LVEF: Left ventricular ejection fraction, *Positive correlation

Correlations between the 3D-LVEF and different parameters

There was a weakly positive correlation between 3D LVEF and MUGA LVEF at the value of (r=0.395, P = 0.031) and a weakly negative correlation with LDL at a value of (r=0.378, P = 0.039) and, as shown in Table 7.

DISCUSSION

Subclinical myocardial involvement in type 2 patients with diabetes has been proved as a form of subclinical LV and RV systolic dysfunction.[7]

Our results agreed with that of Labombarda *et al*.[9] who, suggested that LV longitudinal function is impaired in patients with T2D, and glycemic control may be the main risk factor for the myocardial changes. In contrast, the same time, our results disagreed with Di Cori *et al*.,[10] who did not find a relationship between HbA1c and LV systolic strain.

In our study, we found that the LVEF by MUGA was below normal in 16.67% of the patients with diabetes.

There was a little difference between our result and that of Hazra *et al*.,[11] who studied thirty type 2 subjects with diabetes without cardiac symptoms and thirty prediabetic who were assessed by MUGA and pulse rheography, the LVEF was below normal in 29% of diabetics and 16.6% of prediabetic. Our explanation to this difference is that most of our patients were under strict control of their diabetes as their HbA1c was 6.7 ± 1.2%.

In our study results, we found that there was no correlation between 2DE EF% and that by MUGA and this finding was concordant to the finding of Naik *et al*.,[12] who compared 2DE and MUGA in the determination of LVEF and concluded that the 2D method demonstrated these results because of its geometric assumptions for assessing LVEF.

In our study, we found that all patients with impaired MUGA LVEF had impaired LV-GLS and we found that even in patients with diabetes with preserved LVEF by MUGA, 72% had impaired LV-GLS. On the other hand, Ernande *et al*.,[13] results were discordant with our; they found that only 23% (14/60) of study diabetic patients with impaired LVEF by MUGA had LV longitudinal systolic dysfunction determined as their LV-GLS < -18, and our explanation to our finding is the high ability of 2D-STE to predict subclinical LV systolic dysfunction, which is unmasked by the alteration of longitudinal strain.[14]

Also, we found a moderately positive correlation between EF by MUGA and LV-GLS. Gopal *et al*.[15] in 1995 conducted a comparative study between 3DE and MUGA. In that study, LVEF measured by MUGA ranged from 9% to 75%, with a mean of 47% ± 19%, they showed an excellent correlation between the

3DE method and MUGA and this was consistent with our results as we found a 60% of patients with impaired MUGA LVEF with impaired 3D LVEF and we found a weakly positive correlation between these two methods.

We found that even in patients with diabetes with preserved LVEF by MUGA, 56% had impaired 3D LVEF. In our study, we found a statistically significant reduction in the LV-GLS in the group with diabetes compared to in the control group. Moreover, LV-GLS was lower in the diabetic group with impaired MUGA LVEF. Also, LV-GLS was lower in the diabetic group with impaired 3D LVEF, and all those patients with preserved 2D LVEF being concordant to our results the result of Nakai *et al*., [14] they reported that GLS in patients with diabetes mellitus (DM) was significantly lower than that in age-matched normal subjects despite of similar 2D LVEF, and 43% (26/60) of patients with DM showed LV longitudinal systolic dysfunction determined as GLS <17.2%.

Mochizuki *et al*.[16] studied 144 patients with diabetes without overt heart failure or and cardiac disease including type 1 and type 2 patients with diabetes found that 37% of the patient group had reduced GLS, but this result was associated with diabetic complications, especially diabetic nephropathy and neuropathy and hypertriglyceridemia.

Jędrzejewska *et al*. [17] studied LV in 50 patients with type 2 DM (T2DM) and found that there was a statistically significant reduction in LVGLS in the patients with diabetes compared with the control group.

Some studies have explained the pathophysiological causes of LV longitudinal dysfunction in patients with DM patients as microvasculopathy, myocardial hypertrophy, and cardiac fibrosis due to hyperinsulinemia, and dysregulation of the extracellular matrix due to hyperglycemia.[18]

Ceyhan *et al*.[19] found that all LV-GLS were reduced in patients with uncontrolled DM, which is consistent with our study results.

In our study, a significant correlation between LV-GLS and HbA1c was observe; our results agreed with Labombarda *et al*. [9] who, suggested that LV longitudinal function is impaired in patients with T2D, and glycemic control may be the main risk factor for the myocardial changes. This finding was discordant with Di Cori *et al*., [10] who did not find a relationship between HbA1c and LV systolic strain or velocity.

Wang *et al*.[20] studied 82 patients with type 2 diabetes including 46 subjects with diabetes alone and 36 subjects with diabetes and hypertension; their study results showed that despite a similar 2D LVEF, 3D LVEF was significantly lower in patients with diabetes only than in control ($P < 0.001$). We agree with that, as in our study results, we found a significantly lower 3D LVEF in patients with diabetes than in control and all those patients were with preserved 2D LVEF, 94% impaired LV-GLS, and 17.6% with impaired MUGA LVEF. Vinereanu *et al*.[21] observed an inverse correlation between LDL and subclinical left ventricular dysfunction by real-time 3D echocardiography and found that LDL was an independent determinant of systolic function. In our study, a weakly negative correlation between 3D LVEF and LDL was observed, and this was concordant with the result of the previous study.[21]

Study limitations

The main limitation is the limited number of patients studied; further studies including a larger number of patients might be needed in the future.

CONCLUSION

T2DM is associated with subclinical left ventricular systolic dysfunction that can be assessed by different non-invasive modalities (speckle tracking, 3D echocardiography and MUGA scan). New noninvasive modalities like speckle tracking and 3D echocardiography might be more powerful than MUGA scan in the detection of subclinical left ventricular systolic dysfunction, for further evaluation. Therefore, we recommend that STE should be considered a routine investigation in the assessment of patients with T2DM.

Ethics

Ethics Committee Approval: The study was approved by the Ethical Committee of Al-Azhar University Faculty of Medicine for Girls, approval number 202209/543 (date: 28.09.2022).

Informed Consent: All patients included in the study accepted oral and written consent.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: T.A., M.N., T.S., Concept: T.A., M.N., T.S., Design: T.A., M.N., T.S., Data Collection or Processing: T.A., M.N., T.S., Analysis or Interpretation: M.Z., Literature Search: M.Z., Writing: M.Z.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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RESEARCH ARTICLE

DOI: 10.4274/ijca.57966
Int J Cardiovasc Acad 2023;9(1):16-19

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.

To cite this article: Doğan Y, Turunç Özdemir A. Assessment of Carotid Intima-media Thickness in COVID-19 Survivors. Int J Cardiovasc Acad 2023;9(1):16-19

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Received: 28.03.2023
Revised: 29.03.2023
Accepted: 29.03.2023
Published Online: 14.04.2023

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.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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CASE REPORT

DOI: 10.4274/ijca.55264
Int J Cardiovasc Acad 2023;9(1):20-23

A Rare Cause of Secondary Hypertension: Nutcracker Syndrome

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Abstract

Left renal vein entrapment syndrome also known as nutcracker syndrome (NCS) is a vascular anomaly that occurs due to compression of the left renal vein from the outside, causing reduced left renal venous blood flow and thus venous congestion. This may be either asymptomatic or present with various clinical scenarios but is rarely associated with hypertension (HT). In this paper, we report an NCS case diagnosed in a young female patient who presented with HT.

Keywords: Nutcracker syndrome, hypertension, left renal vein

INTRODUCTION

Left renal vein (LRV) entrapment syndrome also known as nutcracker syndrome (NCS), is a vascular anomaly that occurs due to compression of the LRV from outside, causing reduced left renal venous blood flow and thus venous congestion. In this paper, we report an NCS case diagnosed in a young female patient who presented with hypertension (HT).

CASE REPORT

A 45-year-old female patient without a history of HT presented with intermittent high blood pressure readings and headache for the last 1 year. Physical examination showed blood pressure readings of 150/90 mmHg in both arms and a pulse rate of 80 bpm. The patient denied taking any herbal product, licorice or any regular medication, nor she had episodes of diarrhea and flushing. The body mass index was 23 kg/m^2. Physical examination of other systems was normal. Transthoracic echocardiographic examination revealed no pathological conditions except for left ventricular diastolic dysfunction. Routine biochemistry, complete blood count, and thyroid function tests were within normal limits. Urinalysis was normal. Ambulatory blood pressure measurement showed episodes of HT during daytime when the patient was in the erect position for long periods. Daytime mean blood pressure reading was 145/90 mmHg. Both kidneys had a normal size and parenchymal thickness on abdominal ultrasonography (USG). Renal Doppler USG showed that the LRV was compressed between the superior mesenteric artery and abdominal aorta. A computerized tomography angiogram showed that the LRV was compressed between the superomedial mesenteric artery and the aorta [Figures 1-3]. The narrowest segment of LRV having a diameter of 2.3 mm and immediately proximal to that point, the renal vein was dilated, and had a diameter of 12.2 mm [Figure 4]. The LRV diameter ratio was 5.3. The aorto-mesenteric angle was 18° [Figure 5]. In addition, there was dilation in the left gonadal vein. There were no other findings or laboratory parameters to suggest other causes of secondary HT in the patient. The patient was diagnosed with NCS. Target blood pressure could not be achieved by lifestyle modifications.

To cite this article: Uzun G, Sayın MR. A Rare Cause of Secondary Hypertension: Nutcracker Syndrome. Int J Cardiovasc Acad 2023;9(1):20-23

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Received: 07.02.2023
Revised: 28.03.2023
Accepted: 29.03.2023
Published Online: 14.04.2023

She was started benidipine 8 mg once per day. At the clinical follow-up, her blood pressure was regulated, and no additional problem was observed. Informed consent was obtained from the patient.

DISCUSSIONS

LRV entrapment syndrome is characterized by external anatomic compression of the renal vein causing marked dilation of the hilar portion and narrowing of the para-aortic portion of the latter, which results in altered flow dynamics in the inferior vena cava. When symptoms are absent despite the presence of anatomic hallmarks of the condition, it is called the nutcracker phenomenon. NCS refers to renal vein entrapment with well-known associated symptoms, the severity of which is dictated by the seriousness of anatomic compression and hemodynamic perturbation.[1] LRV is usually entrapped anteriorly, between the superior mesenteric artery and the aorta, or less commonly posteriorly, between the aorta and the vertebral column. Our patient had the more common anterior type.

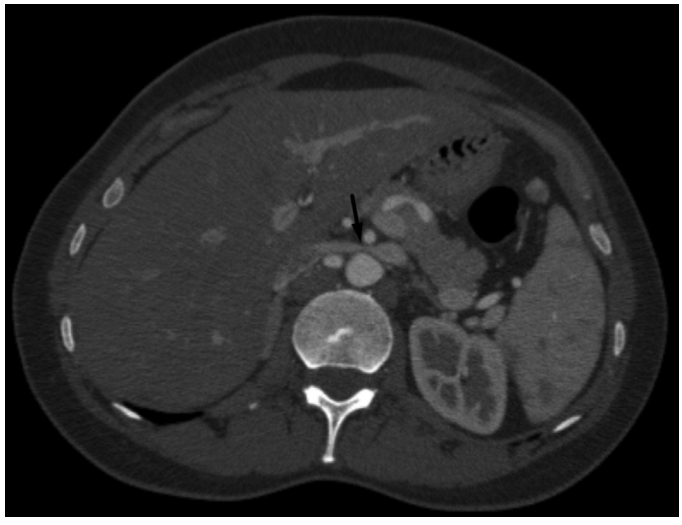

Figure 1: Axial plane of computerized tomographic angiography images of the left renal vein

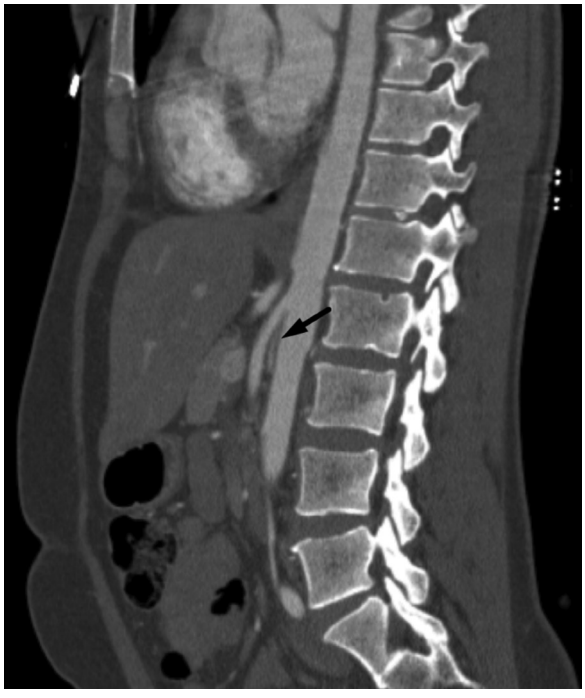

Figure 2: Sagittal plane of computerized tomographic angiography images of the left renal vein

The major clinical signs and symptoms of NCS include mild hematuria, orthostatic proteinuria, flank/abdominal pain, varicocele, and pelvic congestion syndrome.[1] All anatomic variations in the syndrome cause limited outflow in LRV with resultant left renal venous HT. The latter causes hematuria by

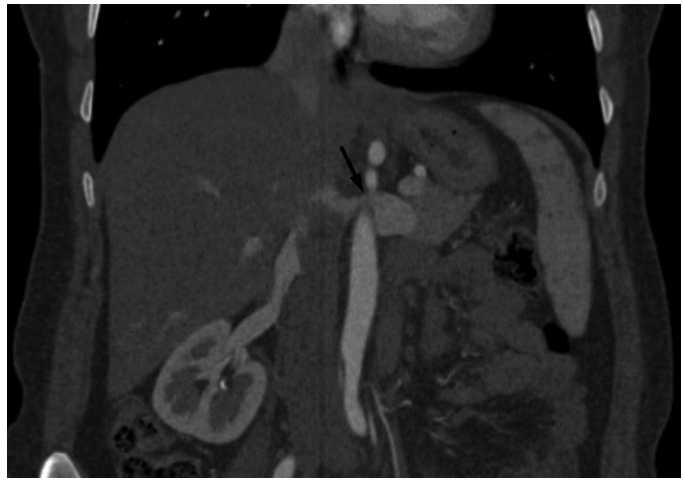

Figure 3: Coronal plane of computerized tomographic angiography images of the left renal vein

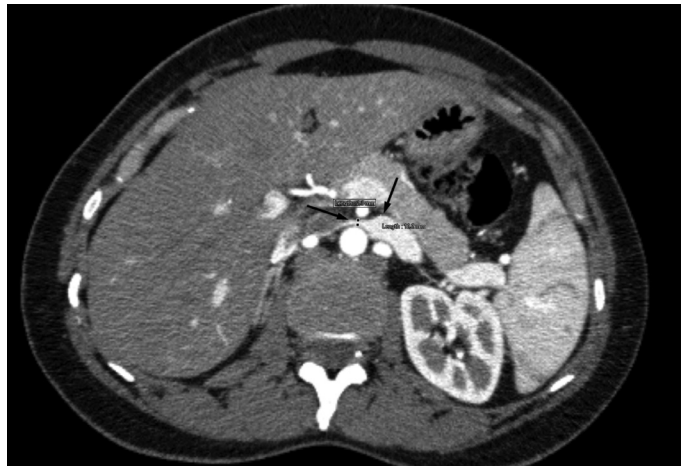

Figure 4: Left renal vein diameter ratio

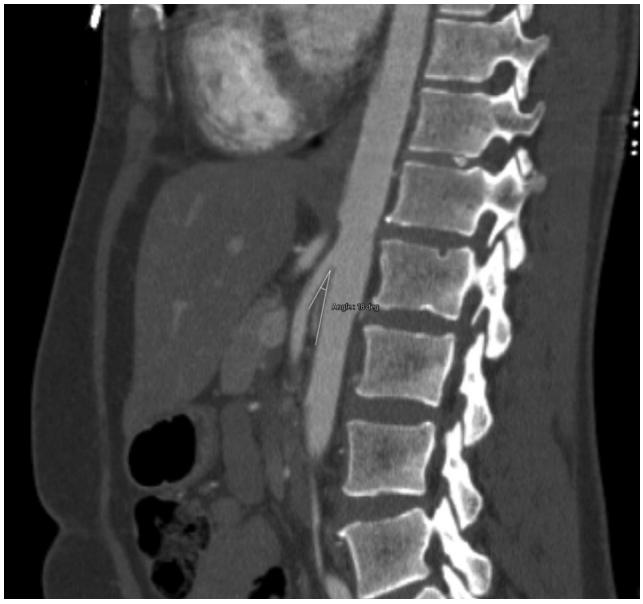

Figure 5: The aorto-mesenteric angle

disrupting the thin septum between small-caliber veins and the collecting system within the parenchyma of the kidney.[1] Patients with fully functional collateral circulation reducing LVR may explain the absence of symptoms. The left gonadal vein draining into the LRV in men may be congested and cause varicocele while women may suffer pelvic congestion syndrome characterized by dysmenorrhea, dysuria, dyspareunia, and pelvic pain.[1]

The syndrome excludes HT as a hallmark sign, which has been reported only rarely. There are several hypotheses why HT develops in this syndrome. These include: 1. Impaired sodium excretion ability of the kidney owing to elevated glomerular pressure resulting from the impedance to blood flow through the LRV; 2. Kidney ischemia and hypoxia secondary to elevated LRV pressure, 3. Renal chemoreceptors and baroreceptors respond to altered glomerular hemodynamic and metabolic milieu and send afferent impulses to the hypothalamus to increase the production and release of norepinephrine, a potent vasoconstrictor.[2,3] Of particular note, our patient presented with an uncommon sign of NCS, i.e, persistently elevated blood pressure and associated headache. As evidenced by normal serum, urinary biochemical tests, as well as imaging studies, she was free of any underlying etiology causing secondary HT such as renal parenchymal disease, hypercortisolism, or adrenal cortical or medullary tumors. She was thus deemed to have no identifiable cause of HT. As a matter of the fact that her LRV was compressed, we made a provisional diagnosis of NCS-associated HT. In the literature, different clinical presentations and treatment modalities exist for NCS cases accompanied by HT. In two reports, NCS was accompanied by HT in two young patients.[4,5] In both these cases, a significant increase was found in blood renin activity, aldosterone concentration, and angiotensin I/II concentrations. They had persistently elevated blood pressure readings despite medical therapy. The patients became normotensive immediately after they received an endovascular stent. In contrast, another case of NCS presented with medically controllable HT despite elevated renin level.[6] Blood pressure control was satisfactorily achieved by medications in the other NCS cases reported in the literature, who had no increased hormone levels.[7-9] Our patient also had normal biochemical parameters. Blood pressure was successfully controlled by medical therapy. Headache was attributed to HT since it improved with blood pressure regulation. However, it should be remembered that NCS associated with headache has also been reported in the literature.[10]

The way a patient with the condition presents and the degree of left renal venous HT usually dictate the management principles. While conservative management is usually employed for mild cases, decompressing the LRV is the main aim in severe cases presenting with persistent hematuria, severe pain, or pelvic congestion syndrome. Satisfactory results have been attained by a variety of treatment modalities including surgical techniques, even renal autotransplantation as well as endovascular stenting to relieve compression. Also in our patient, both blood pressure were brought under control with medical therapy and headache did not recur. Interventional treatments may be considered in cases resistant to medical therapy. NCS may be a difficult-to-diagnose syndrome due to various factors. Decisions regarding treatment should be made on the basis of symptom severity, the reversibility of the condition, patient's age, and disease stage.

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