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The predictive value of the uric acid/albumin ratio in the phenomenon of coronary slow flow

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Abstract

Aim: Inflammation, oxidative stress, and suboptimal endothelial function have all been implicated in the development of coronary slow flow (CSF) in previous studies. Inflammation has been associated with atherosclerosis, endothelial dysfunction, and microvascular coronary dysfunction. In this situation, it is suspected that albumin and uric acid (UA) are related to the cause of CSF. This study compared the uric acid to albumin ratios (UAR) in coronary arteries with angiographically normal coronary arteries to those in CSF patients.

Materials and Methods: In a case-control research, 230 individuals with CSF and an additional 230 individuals who were matched for age, gender, and coronary angiography confirmation to have normal results participated. Retrospective evaluation of 5500 individuals who underwent coronary angiography at our hospital between January 2015 and August 2020 for known or suspected ischemic heart disease was done in this study. Prior to the coronary angiography, our clinic measures basal UA and albumin. By dividing uric acid by albumin, UA/A was calculated. Thrombolysis in Myocardial Infarction Frame Count was used to measure the CSFP.

Results: In order to determine UAR, uric acid to albumin was divided. UAR was substantially higher in the CSF group than in the control group (1.180.21 and 1.50.33, respectively, $p<0.001$). We tested whether UAR predicted independently of CSF presence using multiple logistic regression analysis. The cut-off values used by the UA/effective Albumin have sensitivity and specificity of >1,29 and 81% and 70%, respectively, for predicting the presence of CSF. In comparison to uric acid or albumin alone, UAR had a higher diagnostic accuracy to predict CSF (UA AUC:075, albumin AUC:0,552, and UAR AUC:0,826, respectively).

Conclusion: We found that patients with CSF had greater levels of UAR than subjects with normal coronary arteries. This was the first study to show that UAR was an independent predictor of CSF.

Introduction

Coronary slow flow (CSF), a condition of the heart characterized angiographically by delayed contrast opacification of the distal coronary arteries in the absence of obstructive coronary artery disease (CAD) [1,2]. CSF is found in approximately 1% to 3% of patients undergoing coronary angiography. The first case of CSF was reported in 1972 by Tambe [3].The etiopathogenesis of CSF is unknown. Numerous researches have looked at the connection between endothelial dysfunction and coronary slow flow as a potential reason. It is well accepted that endothelial dysfunction, oxidative stress, and inflammation have a role in the development of CSF [4].

Uric acid is the final byproduct of purine metabolism. Numerous researches [5] have shown that UA levels in the blood are a major and independent risk factor for cardiovascular disease. A higher UA has been associated with endothelial dysfunction [6], antiproliferative effects, increased oxidative stress, the creation of free radicals, and thrombus formation, all of which encourage atherosclerosis and its consequences.

The primary blood protein albumin, which is found in the extracellular liquid compartment, has a variety of phys-

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iological actions [7]. It is thought that the plasma albumin concentration is connected to inflammatory and hemostatic processes [8]. A key player in platelet-mediated coronary artery constriction, albumin is also a potent inhibitor of platelet activation and aggregation [8]. Many studies have shown that low serum albumin levels are associated with higher cardiovascular mortality and morbidity [9].

We hypothesized that an elevated UAR may be connected to the existence of isolated CSF given that the isolated CSF mechanism is caused by increased inflammation and that albumin and UA are both markers of inflammation. A real-world population undergoing coronary angiography for possible or confirmed ischemic heart disease was utilized to identify this.

Materials and Methods

Study population

A total of 5,500 individuals who had coronary angiography (CAG) between January 2015 and August 2020 were assessed retrospectively in this study. The patients were divided into two groups, with and without CSF. All coronary angiograms (5,500 patients) performed in our clinic for 5 years were examined and CSF was detected in 230 patients. 230 age, gender and clinically similar patients were determined as the control group. There were 230 patients with CSF (CSFP) (4.1%) defined as group 1 (group 1, 56 percent male; mean age 55.4±5.8). Group 2 consisted of 230 patients with angiographically normal coronary arteries (62.2 percent male, mean age 54.6±4.8).

Acute coronary syndrome, substantial valvular heart disease, decompensated heart failure, cancer, renal or hepatic failure, acute or chronic infectious disease, autoimmune disease, anemia hematologic disease and acute or chronic pulmonary disease were all exclusion criteria.

The Judkins technique was used to perform coronary angiograms utilizing a femoral approach without the use of nitroglycerin, adenosine, or a calcium channel blocker. Following adequate patient preparation, all patients in the study population received elective coronary artery angiography with the Siemens Axiom Artis DFC (Siemens Medical Solutions, Erlangen, Germany). An automatic injector injected contrast media (Iopromide, Ultravist-370; Schering AG, Berlin, Germany) at 3 to 4 mL/s for left coronary artery and 2 to 3 mL/s for right coronary artery arteriographies, which were recorded at 30 frames/s.

Smoothness of angiography, luminal wall abnormalities, epicardial local or diffuse caliber reduction, and stenosis were considered as all factors. Normal coronary arteries were determined by ocular inspection for the lack of any luminal abnormalities. Patients with normal coronary arteries received a hyperventilation test during coronary arteriography to rule out the possibility of coronary artery vasospasm, which was performed by asking them to breathe quickly and deeply for 5 minutes.

Definitions of CSF

The diagnosis of CSF was given to all patients whose corrected thrombolysis in myocardial infarction frame count (TFC) was more than two standard deviations outside the normal reported range for the specific vessel, as opposed to the diagnosis of normal coronary flow for patients whose corrected TFC was within the published normal range. It was determined how many cine frames at a speed of 30 frames per second were required for the contrast to initially arrive at the typical distal coronary landmark in the left anterior descending (LAD), left circumflex (LCx), and right coronary artery (RCA). The distal bifurcation of the LAD, the distal bifurcation of the segment with the longest total distance for the LCx, and the first branch of the posterolateral artery for the RCA were predefined distal landmarks. Individuals were considered as having a CSF if their TFC was more than 2 standard deviations outside of the reported normal range for any one of the three coronary arteries (>40.6 frames for LAD, >29.8 frames for LCx, and >27.3 frames for RCA).

Laboratory measurements

In our hospital premises, samples of blood were collected from the ante-cubital vein prior to the CAG and were sent to the laboratory within an hour after collection for analysis. Hematology analyzers used the CBS to evaluate the hematologic indices (Beckman Coulter Ireland Inc. Mervue, Galway, Ireland).Blood samples were obtained from patients in the morning, after 12 hours of fasting, for measurement of biochemistry panel including lipid parameters before the index coronary angiography in all patients. Uric acid was divided by albumin to get UAR.

Statistical analysis

Continuous variables were presented as means ± standard deviations if normally distributed and medians [interquartile ranges (IQRs)] if not normally distributed, while categorical variables were given as percentages. The chi-squared (χ^2) test was used to compare categorical variables between the groups, while the Kolmogorov–Smirnov test was employed to assess whether the variables were normally distributed. A Student's t-test or Mann–Whitney U test was used to compare the continuous variables between the groups according to whether they were normally distributed or not. In order to determine the independent predictors for the slow flow, variables found to be associated at a $p<0.05$ level according to univariate analysis, were included in the multivariate logistic regression analysis with the results reported as the odds ratios (OR) and 95% confidence intervals (CI). The discriminatory ability of UAR, uric acid and albumin in determining the slow flow was analyzed by using the receiving operating characteristic (ROC) curve and area under the curve (AUC), accompanied by 95% confidence interval. The optimal cut-off value was also calculated from the point of maximal sensitivity and specificity. The threshold of statistical significance was established at $p<0.05$. All statistical analyses were performed using the Statistical Package for the Social Sciences version 24.0 software program (IBM Corp, Armonk, NY, USA).

Results

Basal characteristics, laboratory, and angiographic findings of all cases were summarized in Table 1. Regarding age, gender, diabetes, hyperlipidemia, body mass index

Table 1. Demographic, clinical and laboratory parameters of the study cohort grouped according to the presence of slow flow.

Variables	All population	Non-SF (n = 230)	SF (n = 230)	p
Male gender, n %	272 (59.1)	143 (62.2)	129 (56)	0.208
Age	55.0±5.3	54.6±4.8	55.4±5.8	0.119
BMI (kg/m^2)	26.7±3.3	26.6±3.0	26.8±3.2	0.353
HT, n (%)	174 (37.8)	69 (30)	105 (45.6)	0.001
DM, n (%)	150 (32.6)	62 (26.9)	88 (38.2)	0.017
Dyslipidemia, n (%)	248 (53.9)	119 (51.7)	129 (56)	0.339
Smoking, n (%)	133 (28.9)	65 (28.2)	68 (29.5)	0.801
Family history, n (%)	155 (33.6)	73 (31.7)	82 (35.6)	0.438
Acetylsalicyclic acid	31 (6.7)	10 (4.3)	21 (9.1)	0.071
RAS-blockers	108 (23.4)	59 (25.6)	49 (21.3)	0.360
Statins	51 (11)	25 (10.8)	26 (11.3)	0.860
Creatinine	0.83 ± 0.22	0.82 ± 0.23	0.85 ± 0.22	0.128
TC, mg/dL	206 ± 49	206±49	206±48	0.911
LDL-C, mg/dL	130 ± 45	128±45	131±46	0.530
HDL-C, mg/dL	43 ± 7.9	46±3.6	39±9.5	<0.001
Triglyceride, mg/dL, median, [IQR]	165 [115-244]	165 [113-245]	166 [113-245]	0.929
WBC	7.8±1.0	7.7 ±1.0	7.9± 1.1	0.072
Hgb	14.2 ±1.2	14.1±1.2	14.2±1.1	0.535
Platelet	287±45	284±47	291±43	0.111
CRP, median, [IQR]	0.70 [0.40-0.80]	0.50 [0.40-0.80]	0.80 [0.50-0.90]	0.002
Uric acid	4.4±0.9	4.0±0.8	4.8±0.9	<0.001
Albumin	3.4±0.63	3.5±0.65	3.3±0.6	0.009
				<0.001
Angiographic parameters				
LAD, n (%)		0 (0)	125 (54.3)	
Cx, n (%)		0 (0)	60 (26.1)	-
RCA, n (%)		0 (0)	45 (19.6)	
LAD TFC		27.3 ± 4.1	47.5± 6.4	<0.01
Cx TFC		23.1 ± 3.5	28.5 ± 8.7	<0.01
RCA TFC		19.6 ± 3.3	28.4 ± 8.4	<0.01

†Continuous variables were presented as means ± standard deviations if normally distributed and medians [interquartile ranges (IQRs)] if not normally distributed, while categorical variables were given as percentages.

Abbreviations: BMI, body mass index; HT, hypertension; DM, diabetes mellitus; RAS, renin angiotensin system; FBG, fasting blood glucose; TC, total cholesterol, LDL-C, low-density lipoprotein cholesterol, HDL-C, high-density lipoprotein cholesterol; CRP, C-reactive protein; UA, uric acid to albumin ratio, RCA, right coronary artery; Cx, circumflex artery, LAD, left anterior descending artery, TFC, thrombolysis in myocardial infarction frame count.

(BMI), and smoking, there were no differences between the two groups that were statistically significant, although the CSFP had considerably higher levels of hypertension. Platelet and hgb levels in terms of laboratory findings were comparable in both groups. While WBC counts were similar in the CSFP group compared to the non-CSFP group, serum C-reactive protein (CRP) levels were considerably higher in the CSFP group. Additionally, there was a statistically significant difference between the CSFP group and the non-CSFP group in the median TFC values for all epicardial coronary arteries. Slow flow was most frequently seen in the LAD (54.3%) among all coronary vessels, followed by the Cx (26.1%), and less frequently in the RCA (19.6%). In order to determine the independent predictors of CSF, we carried out a multivariable logistic regression analysis using factors that showed statistically significant correlations in the univariate research.We did not analyze uric acid and albumin along with the UAR parameter in the multivariate regression analysis because we considered that it would have a detrimental impact on the outcomes of the regression analysis given that they were components of UAR. (Table 2).

We used ROC analysis, to assess the diagnostic efficacy and discrimination capacity of albümin, uric asid, and UAR. A ROC curve analysis indicated that UAR >1.29 was an effective cut-off point with 81% sensitivity and 70% specificity for determining whether CSFP was present or not. (AUC: 0.552; 95% CI: 0.750–0.0.826; p<0.001). The AUC of UAR was 0.80, and it outperformed the other two parameters in terms of diagnostic precision and discrimination power (AUC:0.552 for albumin and AUC:0.750 for uric asid) (Figure 1).

Table 2. Factors that were found to be independently associated with the slow flow in univariate and multivariate regression analysis models.

Variables	Univariate OR (95% CI)	p	Model 1 Multivariate* OR (95% CI)	p	Model 2 Multivariate* OR (95% CI)	p
HT	2.002 (1.328-3.018)	0.001	1.531 (0.857-2.736)	0.150	1.699 (0.969-2.978)	0.064
DM	1.633 (1.070-2.494)	0.023	2.567 (1.407-4.684)	0.002	2.552 (1.409-4.623)	0.002
HDL-C	0.867 (0.836-0.899)	<0.001	0.874 (0.838-0.911)	<0.001	0.874 (0.838-0.911)	<0.001
CRP	1.676 (1.147-2.451)	0.008	1.842 (1.170-2.900)	0.008	1.782 (1.169-2.716)	0.007
Uric acid	2.840 (2.205-3.697)	<0.001	7.218 (4.526-11.511)	<0.001	-	-
Albumin	0.659 (0.480- 0.904)	0.010	0.107 (0.054 – 0.209)	<0.001	-	-
UAR	1.064 (1.050 – 1.079)	<0.001	-	-	1.064 (1.048-1.081)	<0.001

*The variables with a p-value of less than 0.05 in the univariate analysis were incorporated into the multivariate cox regression analysis by using Enter method.

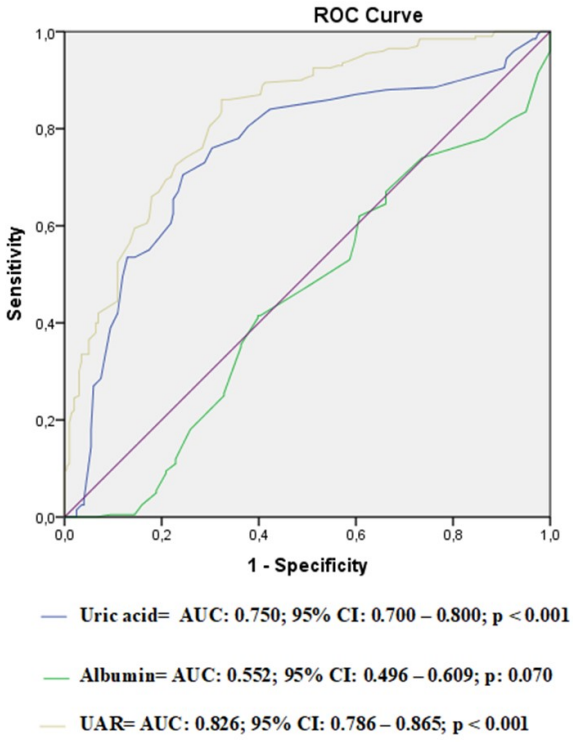

Figure 1. Discriminatory performances of UAR, uric acid and albumin for slow flow. UAR Cut off value = > 1.29 için % 81 sensitivity % 70 specificity.

Discussion

Our data showed that a high UAR was associated with slow flow phenomenon. This report is the first to report a correlation between UAR and slow flow phenomenon. UAR was shown to be significantly greater in patients with CSF, and we also discovered that UAR was connected with CSF phenomena independently. Our results suggest that increased UAR may contribute to the etiology of CSF.

The term "slow coronary flow" is used by interventional cardiologists to characterize substantial epicardial coronary artery opacification that is delayed at the distal parts without any atherosclerotic stenosis [10,11]. Other than a simple definition, the etiopathogenesis is not known. There have been several hypotheses put up on the causes of CSF-like early atherosclerosis, diffuse atherosclerosis, coronary vasomotor dysfunction, and altered endothelial activity [11]. Additionally, systemic inflammation as well as oxidative stress may contribute to the pathophysiology of the CSF. Li et al. [11] found that CRP and interleukin 6 levels were significantly higher in CSF patients [12]. Barutcu et al. [13] also found that hsCRP, a well-known measure of systemic inflammation, is linked to the prevalence of CSF or plays a role in its etiology.

Uric acid is a byproduct of the purine metabolism. Therefore, increased levels of uric acid in the blood indicate oxidative stress and endothelial dysfunction. By lowering oxidative stress, which results in endothelial dysfunction, the xanthine oxidase inhibitor allopurinol, which is used to treat hyperuricemia, has been demonstrated to minimize brachial artery flow-related dilatation [14]. The presence of CSF has also been related in previous studies to increased oxidative stress and endothelial dysfunction [15].

In our patient group, uric acid levels were slightly higher in patients with slow coronary flow compared to patients without coronary slow flow. The relationship between serum uric acid levels and cardiovascular risk has been studied by experts for many years. Although some researches have produced contradictory results, many have discovered a connection between serum uric acid (SUA) and cardiovascular disease. On the other hand, current meta-analyses of prospective studies have proven that hyperuricemia is a distinct risk factor for cardiovascular disease. Zuo et al. performed a meta-analysis of 14 prospective trials with 341,389 adult participants. Patients with hyperuricemia had a greater relative risk of dying from coronary heart disease, researchers found (CHD) [16]. In addition, Li et al. found in a meta-analysis of 29 prospective cohort studies that hyperuricemia was associated with an increased risk of CHD morbidity and death [17]. A fundamental protein called albumin participates in both acute and chronic inflammatory processes, controls plasma oncotic pressure, and functions as a drug transporter. Increased capillary loss (especially renal), decreased hepatic synthesis, acute or chronic inflammatory processes, and increased plasma volume in cases of malabsorption or malnutrition are the causes of hypoalbuminemia [18]. Serum albumin is thought to be an anti-inflammatory and anti-atherogenic biomarker since it inhibits TNF-induced VCAM-1 expression, nuclear factor-B activation, and monocyte cell adhesion in aortic endothelial cells [19].

Lower serum albumin levels have been associated with increased systemic inflammatory load. Proinflammatory cytokines have been associated with a drop in albumin levels. Inflammatory diseases have been associated with increased albumin catabolism and decreased albumin synthesis. In a recent study, Cetin et al. found that patients with CSF had lower serum albumin levels than those with typical coronary arteries [20]. Yang et al. reported that uric acid levels were positively correlated and albumin levels negatively correlated with CSF [21]. In parallel with these results, in our study, serum albumin levels were found to be lower in the patient group with slow coronary flow than those without slow flow. These results were supported by the discovery that blood albumin levels were lower in patients with CSF than in those with conventional coronary arteries. We expected that UAR would be higher in patients with CSF because there was evidence of a close link between the CSF phenomena and inflammation.

Finally, we found that UAR levels were considerably higher in CSF patients than in the general population. These results imply that CSF and CAD have similar pathophysiological processes. More research with a bigger sample size is required to determine the precise functions of these markers in common pathophysiological pathways.

Declaration of conflicting interest

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Ethical approval

Ethics committee approval was obtained from the ethics committee unit of Istanbul Haseki Training and Research Hospital, dated 14.12.2022 and numbered 213-2022.

References

1. Beltrame JF, Limaye SB, Horowitz JD. The coronary slow flow phenomenon: a new coronary microvascular disorder. Cardiology. 2002;97(4):197–202. Google Scholar | Crossref | Medline | ISI.
2. Beltrame J, Ganz P. The coronary slow flow phenomenon. In: Kaski, J, Eslick, G, Bairey Merz, C (eds). Chest Pain with Normal Coronary Arteries. London: Springer; 2013:101–117. Google Scholar | Crossref.
3. Tambe AA, Demany MA, Zimmerman HA, Mascarenhas E. Angina pectoris and slow flow velocity of dye in coronary arteries—a new angiographic finding. Am Heart J. 1972;84(1):66–71.
4. Enli Y, Turk M, Akbay R. Oxidative stress parameters in patients with slow coronary flow. Adv Ther. 2008;25(1):37–44Google Scholar | Crossref | Medline | ISI.
5. Freedman DS, Williamson DF, Gunter EW, Byers T. Relation of serum uric acid to mortality and ischemic heart disease. The NHANES I Epidemiologic Follow-up Study. Am J Epidemiol 1995;141:637-44.
6. Diaz M. N , Frei B, Vita J. A. and Keaney Jr., "Antioxidants and atherosclerotic heart disease," The New England Journal of Medicine, vol. 337, no. 6, pp. 408–416, 1997. View at: Publisher Site | Google Scholar.
7. Peters T . Serum albumin. Adv Protein Chem. 1985;37:161–245Google Scholar | Crossref | Medline.
8. Danesh J, Collins R, Appleby P, Peto R. Association of fibrinogen, C-reactive protein, albumin, or leukocyte count with coronary heart disease: meta-analyses of prospective studies. JAMA. 1998;279(18):1477–1482. Google Scholar | Crossref | Medline | ISI.
9. Gresele P, Deckmyn H, Huybrechts E, Vermylen J. Serum albumin enhances the impairment of platelet aggregation with thromboxane synthase inhibition by increasing the formation of prostaglandin D2. Biochem Pharmacol. 1984;33(13):2083–2088Google Scholar | Crossref | Medline | ISI.
10. Yucel H, Ozaydin M, Dogan A. Plasma concentrations of asymmetric dimethylarginine, nitric oxide and homocysteine in patients with slow coronary flow. Scand J Clin Lab Invest. 2012;72(6):495–500. Google Scholar | Crossref | Medline | ISI.
11. Erdogan D, Caliskan M, Gullu H, Sezgin AT, Yildirir A, Muderrisoglu H. Coronary flow reserve is impaired in patients with slow coronary flow. Atherosclerosis. 2007;191(1):168–174. Google Scholar | Crossref | Medline | ISI.
12. Li JJ, Qin XW, Li ZC. Increased plasma C-reactive protein and interleukin-6 concentrations in patients with slow coronary flow. Clin Chim Acta. 2007;385(1-2):43–47. Google Scholar | Crossref | Medline | ISI.
13. Barutcu I, Sezgin AT, Sezgin N. Increased high sensitive CRP level and its significance in pathogenesis of slow coronary flow. Angiology. 2007;58(4):401–407. Google Scholar | SAGE Journals | ISI.
14. Farquharson CA,Butler R,Hill A,Belch JJ,Struthers AD.Allopurinolimproves endothelial dysfunction in chronic heart failure. Circulation 2002;106:221-6.
15. Jaramillo M, Naccache PH, Olivier M. Monosodium urate crystals synergize with IFN-gamma to generate macrophage nitric oxide: involvement of extracellular signal-regulated kinase 1/2 and NF-kappa B. J Immunol 2004;172:5734-42.
16. Zuo T, Liu X, Jiang L, Mao S, Yin X, Guo L. Hyperuricemia and Coronary Heart Disease Mortality: A Meta-Analysis of Prospective Cohort Studies. BMC Cardiovasc. Disord. 2016;16:207. doi: 10.1186/s12872-016-0379-z. [PMC free article] [PubMed] [CrossRef] [Google Scholar] [Ref list].
17. Li M, Hu X, Fan Y, Li K, Zhang X, Hou W, Tang Z. Hyperuricemia and the Risk for Coronary Heart Disease Morbidity and Mortality a Systematic Review and Dose-Response Meta-Analysis. Sci. Rep. 2016;6:19520. doi: 10.1038/srep19520. [PMC free article] [PubMed] [CrossRef] [Google Scholar] [Ref list].
18. Don BR, Kaysen GA. Serum albumin: relationship to inflammation and nutrition. Semin Dial. 2004;17(6):432–437. Google Scholar | Crossref | Medline | ISI.
19. Zhang WJ, Frei B. Albumin selectively inhibits TNF alpha-induced expression of vascular cell adhesion molecule-1 in human aortic endothelial cells. Cardiovasc Res. 2002;55(4):820–829. Google Scholar | Crossref | Medline | ISI.
20. Cetin M, Zencir C, Tasolar H, Baysal E, Balli M, Akturk E. The association of serum albumin with coronary slow flow. Wien Klin Wochenschr. 2014;126(15-16):468–473. Google Scholar | Crossref | Medline.
21. Yang Z, Jiansong Y, JinGang C, Hao G, and Shubin Q. Association of the lymphocyte-to-monocyte ratio, mean diameter of coronary arteries, and uric acid level with coronary slow flow in isolated coronary artery ectasia. BMC Cardiovasc Disord. 2021; 21: 156.