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Title: Increased arterial stiffness – similar findings in patients with inflammatory bowel disease without prior hypertension or diabetes and in patients with well-controlled hypertension

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Increased arterial stiffness – similar findings in patients with inflammatory bowel disease without prior hypertension and diabetes and in patients with well-controlled hypertension

Abstract:

Purpose: Chronic inflammatory diseases are related with earlier onset of atherosclerosis. We hypothesized that inflammatory bowel disease patients with chronic, systemic inflammation have an increased arterial stiffness associated with the disease duration. Also, we wanted to compare arterial stiffness markers between inflammatory bowel disease and well-controlled hypertension patients.

Materials and methods: A total of 89 inflammatory bowel disease patients (60 patients with Crohn's disease and 29 patients with ulcerative colitis, age range 20-64 years) without history of arterial hypertension or diabetes were enrolled and age matched with a control group of patients (73 patients, age range 25-69 years, 41 (56.1%) males) with known history of well-controlled arterial hypertension. We have used a noninvasive device that simultaneously measures brachial blood pressure and estimates PWV and AIx in inflammatory bowel disease and hypertension groups of patients.

Results: Patients with pathological PWV values were significantly older, had significantly longer duration of inflammatory bowel disease, higher values of serum cholesterol and HDL-cholesterol, and higher AIx (17.4% vs. 9.8%) (all $p < 0.05$). Higher PWV was associated with age and duration of inflammatory bowel disease in the linear regression model. PWV values were higher in hypertensive patients in the first two age quartiles while interestingly, in the last two quartiles, PWV was lower than in inflammatory bowel disease group of patients.

Conclusions: Chronic subclinical inflammation is responsible for dyslipidemia and accelerated atherosclerosis which consequently alters arterial elasticity. Inflammatory bowel disease and its duration should also be considered a risk factor for subclinical organ damage, as well as hypertension.

Keywords:

Inflammatory bowel disease; arterial stiffness; arterial hypertension; vascular aging; chronic inflammation; pulse wave velocity

Introduction:

Inflammatory bowel disease is a group of medical conditions characterized by chronic immunologic activation and inflammation of small and large intestine [1]. Higher risk of thromboembolic incidents in inflammatory bowel disease patients has been well researched [2] and found to be especially high during relapse and in chronically active disease [3]. Pivotal role of inflammation mechanisms in the development of atherosclerosis is undisputable and chronic inflammatory diseases are related with earlier onset of atherosclerosis [4–6]. Inflammatory bowel disease usually occurs in younger population in their second and third life decade. Taking latter into consideration, long-standing inflammation and a consequential development of atherosclerosis has a profound medical effect and impact on patient's quality of life [7]. Arterial stiffness is one of the indicators of vascular aging and has an important role in the cardiovascular disease. Measurement of arterial stiffness is used in every-day practice to assess the cardiovascular risk in patients [8,9]. Arterial stiffness depends on age and presence of established risk factors for atherosclerosis such as smoking, hypertension, diabetes and hyperlipidemia [10–14]. Arterial stiffness can be assessed noninvasively by measuring aortic pulse wave velocity (PWV) and augmentation index (AIx), which is shown to have predictive value for future fatal cardiovascular events and for determining cardiovascular risk in the population [15,16]. We hypothesized that inflammatory bowel disease patients with chronic, systemic inflammation have an increased arterial stiffness which is associated with the disease duration rather than the present disease activity. Furthermore, we wanted to evaluate possible difference in arterial stiffness markers, PWV and AIx, between inflammatory bowel disease patients and age and sex matched controls with well-controlled hypertension. The aim of this work was to study the arterial stiffness in relation to inflammatory bowel disease.

Materials and methods:

Study Patients

A total of 89 inflammatory bowel disease patients (60 patients with Crohn's disease and 29 patients with ulcerative colitis, age range 20-64 years) without history of arterial hypertension or diabetes were enrolled and age-matched with a control group of patients (73 patients, age range 25-69 years, 41 (56.1%) males) with known history of well-controlled arterial hypertension. All of the patients in the control group were using antihypertensive medications (ACE-inhibitors, angiotensin II receptor blockers or calcium channel blockers) with no differences in number of antihypertensives per patient and in number of different antihypertensive classes between subgroups of patients divided by age quartiles. All of hypertensive patients had well controlled hypertension. There was no difference between the duration of the inflammatory bowel disease and hypertension in the two groups (122.0+10.2 vs 131.2+11.1 months). Hypertension in inflammatory bowel disease patients was defined as blood pressure levels $\geq 140/90$ mmHg. Exclusion criteria were: amputees, history of mental illness, atrial fibrillation or other chronic arrhythmias, stage III-IV congestive heart failure, liver disease or ascites, diabetes, history of stroke, transient ischemic attack (TIA), myocardial infarction (in the three previous months) or malignant disease. The protocol was approved by the hospital ethics committee, in accordance with the Helsinki Declaration, and all participants gave written informed consent.

Data Collection

The detailed medical history of the patients was collected and a complete physical examination was conducted. In all patients following biochemical data were collected: complete blood count (CBC), C-reactive protein, fibrinogen, serum glucose, lipid profile, sodium, potassium, calcium, phosphorus, blood urea nitrogen (BUN) and creatinine, bilirubin, liver transaminases, gamma-glutamyl transferase (γ GT) alkaline phosphatase, hemoglobin A1c (HbA1c). The activity of Crohn's disease was assessed by Harvey-Bradshaw index while the severity of ulcerative colitis was assessed by Truelove and Witts'

criteria. Target organ damage of the kidneys was determined by measuring creatinine clearance and microalbuminuria in the 24-hour urine sample.

Hamodynamic measurement

The noninvasive measurement of pulse wave velocity, as an index of arterial stiffness, was performed in inflammatory bowel disease group and hypertension group of patients using previously validated, noninvasive device (Tensiomed Arteriograph device (Medexpert Ltd., Budapest, Hungary)), that uses oscillometric method which simultaneously measures brachial blood pressure, PWV and AIx. Measurement was done in a dedicated room in a recumbent position after the 15 minutes rest. PWV and AIx were determined as a mean of three measurements. PWV is low in arteries of normal elasticity and increases in the stiffer (and older) arteries. Recent study reported a mean PWV of 7.8 ± 2.2 m/s in patients with systemic lupus which is a similar disease to inflammatory bowel disease in terms of chronic inflammation and its association with advanced atherosclerosis so we have divided inflammatory bowel disease patients in quartiles depending on different PWV values [17].

Statistical analysis

It was performed using SPSS version 23.0 (IBM Corp., USA). Normality of data distribution was tested using Kolmogorov-Smirnov test. Preliminary analyses were performed to ensure no violation of the assumptions of normality, linearity and homoscedasticity. Categorical data were expressed as numbers and frequencies. Correlations were obtained using Pearson's test for normally distributed variables and Spearman rank correlation for non-normally distributed variables. Normally distributed variables were presented as means + standard deviations and Student's t test for independent samples was used for comparisons between two groups. Non-normally distributed data was presented as median and interquartile range and Mann-Whitney U-test was used in comparison between two groups. Categorical variables were compared using χ^2 - test. Analysis of variance (ANOVA) was used to detect significant differences among \geq two groups. Binary logistic regression was made to assess prediction of elevated PWV levels. Multiple linear regression was used to

explore the influence of different variables on PWV levels. A p value <0.05 (two-sided tests) was considered significant.

Results:

We have enrolled 89 patients (age 34 (20-64); men 52/58.4%). There were no differences in age, gender and smoking status between inflammatory bowel disease patients with Crohn's disease and ulcerative colitis. The differences in duration of inflammatory bowel disease and biochemical data as well as in blood pressure values and arterial stiffness markers AIx and PWV were not found between these two groups of patients. Importantly, significantly higher number of Crohn's disease patients was on immunosuppressant and biologic treatment compared with ulcerative colitis patients. However, when the patients on immunosuppressive and biologic treatment were compared with patients without immunosuppressive and biologic treatment no significant difference in arterial stiffness markers was found. Additionally, we have not found any differences when patients were divided by gender. The patients were divided by the localization of ulcerative colitis, proctitis, left-sided colitis and pancolitis, and although the duration of inflammatory bowel disease was significantly longer in patients with pancolitis we have not found differences in hemodynamic parameters. We have failed to find any differences in patients with different Crohn's disease phenotypes and differences in hemodynamic parameters between patients with different disease activity. Demographic, clinical and biochemical data of inflammatory bowel disease patients are shown in Table 3. (online supplement). Hemodynamic characteristics of inflammatory bowel disease patients are shown in Table 4. (online supplement).

We have divided patients in quartiles depending on different PWV values. Patients in last two quartiles were significantly older than patients in first two quartiles with no differences in duration of inflammatory bowel disease. Patients in the last quartile had higher values of systolic, diastolic and central systolic blood pressure than patients in the first three quartiles while AIx values were higher than in patients in the first two quartiles (Table 2. online supplement). On univariate analysis PWV was positively correlated with age ($r=0.495$; $p<0.001$), duration of inflammatory bowel disease ($r=0.236$; $p=0.03$), central systolic blood pressure ($r=0.478$, $p<0.001$), serum cholesterol ($r=0.304$, $p=0.005$), LDL-cholesterol ($r=0.277$, $p=0.01$) and HDL-cholesterol ($r=0.241$, $p=0.03$) while AIx

was positively correlated with age ($r=0.563$; $p<0.001$), duration of inflammatory bowel disease ($r=0.283$; $p<0.01$), central systolic blood pressure ($r=0.352$, $p=0.001$), serum cholesterol ($r=0.375$, $p=0.001$), LDL-cholesterol ($r=0.346$, $p=0.01$) and HDL-cholesterol ($r=0.272$, $p=0.01$). On logistic regression older patients, patients with longer duration of inflammatory bowel disease and patients with higher values of LDL-cholesterol had OR's for $PWV>8$ m/s of 4.64 [CI 1.01, 1.14], 7.55 [CI 1.00, 1.01] and 4.73 [CI 1.19, 26.8]. In the linear regression model age and duration of inflammatory bowel disease were only and positive predictors of higher PWV ($\beta= 0.452$ and $\beta=0.363$, all $p<0.05$) while we have not found this association with dyslipidemia.

In all group of patients there were 11.2% (10/89) inflammatory bowel disease patients with newly-diagnosed hypertension. Hypertensive inflammatory bowel disease patients had significantly higher PWV values when compared to non-hypertensive patients (9.3 vs. 7.6 m/s; $p<0.003$). We have failed to find any differences in other variables when comparing these two subgroups of patients except longer duration of inflammatory bowel disease in hypertensive patients although statistically insignificant (146.0 vs. 118.9 months). When AIx and PWV were compared between inflammatory bowel disease patients and well controlled hypertensive patients by age quartiles we have found higher AIx values in hypertensive patients in the first two age quartiles while there were no differences between two groups in the last two quartiles (Table 1). There were no differences in PWV values between these two groups of patients except in the last quartile where interestingly PWV was higher in inflammatory bowel disease group of patients. Hypertensive patients had higher central systolic blood and pulse pressure values in the second and third quartile. We have found in the last two quartiles significantly higher total and LDL-cholesterol levels in inflammatory bowel disease group. Duration of hypertension and inflammatory bowel disease were similarly correlated with higher PWV levels (Figure 1).

Discussion:

Increased arterial stiffness is well known marker of subclinical target organ damage and it is strongly and independently associated with increased cardiovascular morbidity and mortality [8,15]. Chronic inflammatory diseases like systemic lupus, vasculitis and rheumatoid arthritis progressively lead to stiffening of large arteries through presence of atherosclerosis and longer duration of the underlying chronic inflammatory disease [5]. Inflammatory bowel disease is associated in many reports with premature atherosclerosis caused by endothelial dysfunction and increased intima-media [18,19]. The prevalence of hypertension, diabetes and dyslipidemia in inflammatory bowel disease is lower when compared to general population, however, cardiovascular risk is increased [20,21]. In many studies one of the possible explanations for this paradox is an increased PWV, which is an independent marker for increased cardiovascular risk in inflammatory bowel disease patients when compared to general population [22–24]. Various risk factors contribute to increased arterial stiffness in inflammatory bowel disease. Beside different therapy, biologic treatment, immunosuppression and corticosteroids, BMI, cytokine levels and C-reactive protein, the duration of inflammatory bowel disease was reported to have a very important association with increased PWV levels [16].

In the last two PWV quartiles, more advanced chronological aging and increased vascular aging as a result of prolonged duration of inflammatory bowel disease are the most plausible explanations for pathological PWV. Interestingly, these patients had not only increased arterial stiffness of large arteries but also AIx. In contrast to previous reports [25], we have not found associations between active disease and increased arterial stiffness but only the duration of the disease as a marker of prolonged inflammation independent of already established risk factors which is similar to the meta-analysis by Zanoli et al [26]. Different Crohn's disease phenotypes and ulcerative colitis localization were not associated with increased PWV. Microalbuminuria and left ventricular hypertrophy as markers of target organ damage were almost not present while increased PWV was present in 40.4% of all inflammatory bowel disease patients. Regarding these results PWV in

inflammatory bowel disease patients should be measured more often as a risk factor for development of cardiovascular disease. In all groups of patients, age, duration of inflammatory bowel disease and dyslipidemia were strong and independent predictors of both increased arterial stiffness markers, PWV and AIx, while interestingly, activity of inflammatory bowel disease, biologic treatment and immunosuppression were not significant predictors at all.

This is the first study, at least to our knowledge, which analyzed and made a comparison of arterial stiffness markers between patients with inflammatory bowel disease and hypertensive patients with already established risk factor for increased arterial stiffness. In all groups of patients we have not found differences in PWV values between patients with inflammatory bowel disease and matched controls with hypertension while hypertensives had higher AIx values. Interestingly, when patients were divided by age quartiles, inflammatory bowel disease patients had higher PWV values in the last two quartiles with no differences in AIx values. This is confirming our presumption that inflammatory bowel disease and its longevity plays a similar role as hypertension, an already established risk factor, for increased arterial stiffness (Figure 1). Furthermore, the presence of dyslipidemia in these last two inflammatory bowel disease patients group quartiles is an additional risk factor for increased arterial stiffness. Age and blood pressure values must be taken into account analyzing arterial stiffness especially in the reference range. Some subjects are at higher risk than others although in the same age group even when PWV is below a cut-off for pathological values. Large study by Mattace-Raso et al. [27] have obtained data of PWV and basic clinical parameters on 1455 patients with optimal blood pressure values from eight European countries and tried to establish normal and reference values of PWV. All age quartiles of inflammatory bowel disease patients from our study had higher PWV in comparison with these reference values as well as with the results from other studies [27–29]. Our results are in line with previous studies which reported higher PWV values in inflammatory bowel disease patients when compared to general population [22–24]. The association of longer duration of inflammatory bowel disease and pathological PWV was stronger than with dyslipidemia and age since older inflammatory bowel disease patients had

higher arterial stiffness markers than hypertensive patients. In the light of these results it can be presumed that arterial stiffness and vascular aging are more pronounced in inflammatory bowel disease patients with longer disease duration compared, not only to healthy controls, but to patients with already established risk factors such as hypertension as well.

Increased arterial stiffness is a well-known characteristic of inflammatory bowel disease patients. Our results on higher PWV and AIx in patients with longer duration of inflammatory bowel disease are in line with our hypothesis that chronic inflammation, regardless of disease activity, is responsible for wall alterations of both large and smaller arteries. Premature atherosclerosis and the presence of dyslipidemia as determinants of increased PWV should be strongly monitored and aggressively corrected especially in patients with longer inflammatory bowel disease duration. This is the first study which analyzed not only arterial stiffness in inflammatory bowel disease patients but also compared its values with hypertensive patients. In this cross-sectional study we confirmed our hypothesis and found that arterial stiffness markers in inflammatory bowel disease patients with longer disease duration were higher than in hypertensive patients.

Our work has several limitations. First, we have enrolled patients from only one inflammatory bowel disease center and our results should be confirmed on larger number of patients. Secondly, although we have analyzed only hypertensives without diabetes and with the same classes of antihypertensive drugs, the markers of inflammation were not analyzed in this matched control group. Therefore, we could not see possible differences in unknown inflammation status between these patients. Thirdly, unfortunately carotid intima media thickness as an additional marker of subclinical organ damage was not analyzed which would additionally improve obtained results. Fourth, we did not analyze possible differences in arterial stiffness markers over time. One could argue that in this study we have seen a strong and independent association of disease duration and increased arterial stiffness but possible increase of arterial stiffness in younger patients over time could be an additional proof for this association. Fifth, the data for future cardiovascular incidents and mortality in this group of patients would be of extreme importance in determining inflammatory

bowel disease duration not only as a marker for increased arterial stiffness but also as a marker for future cardiovascular events. Sixth, PWV was determined using Arteriograph, device which is validated but with no referral cut-off values for inflammatory bowel disease patients. Seventh, although this is the first study which analyzed and compared arterial stiffness between inflammatory bowel disease and hypertensive patients the lack of healthy control group is a limitation factor for this study.

Increased arterial stiffness in inflammatory bowel disease patients is associated with longer disease duration, but not with disease activity. Chronic subclinical inflammation is responsible for dyslipidemia and accelerated atherosclerosis which consequently alters arterial elasticity. Inflammatory bowel disease and its duration should also be considered a risk factor for subclinical organ damage, as well as hypertension. These patients should be monitored very carefully and in larger number for risk stratification for future fatal cardiovascular events.

Declaration of interest

The authors report no conflict of interest.

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Figure 1. Scatter-plot on inflammatory bowel disease and chronic hypertension duration correlation with pulse wave velocity

Inflammatory bowel disease – dark filled circles and full line; Hypertension – white squares and dashed line

Table 1. Differences in demographic, clinical, biochemical and hemodynamic data between inflammatory bowel disease and hypertension patients by age

	Age Quartiles							
	1 Years (18-26)		2 Years (27-38)		3 Years (39-52)		4 Years (53-69)	
	Inflammatory bowel disease (N=22)	Hypertension (N=18)	Inflammatory bowel disease (N=21)	Hypertension (N=17)	Inflammatory bowel disease (N=24)	Hypertension (N=19)	Inflammatory bowel disease (N=22)	Hypertension (N=19)
Males (N/%)	14 (63.6)	10 (55.5)	13 (61.9)	9 (52.9)	14 (58.3)	12 (63.2)	11 (50.0)	10 (52.6)
Smoker (N/%)	1 (4.5)	1 (5.5)	2 (9.5)	2 (11.7)	2 (8.3)	2 (10.5)	2 (9.1)	3 (15.8)
Duration of bowel disease or hypertension (months)	74.0±5.8	102.7±16.3	116.6±17.4	144.7±21.2	135.7±18.9 [^]	79.4±6.9	232.0±35.1	145.3±21.9
Serum cholesterol (mmol/L)	3.07±0.4	2.99±0.3	3.07±0.4	3.01±0.3	4.35±0.5 [*]	3.31±0.4	4.08±0.5 [°]	3.45±0.4
HDL- cholesterol (mmol/L)	0.98±0.2	0.95±0.2	1.06±0.2	0.99±0.2	1.21±0.2	1.05±0.2	1.26±0.2	1.15±0.2
LDL- cholesterol (mmol/L)	1.47±0.3	1.44±0.3	1.55±0.3	1.51±0.3	2.42±0.3 [°]	1.72±0.3	2.92±0.3 [°]	2.13±0.3
Serum triglycerides (mmol/L)	1.15±0.2	1.19±0.2	0.96±0.2	1.05±0.2	1.46±0.2	1.33±0.2	1.29±0.2	1.33±0.2
Systolic blood pressure (mmHg)	124.5±14.4	125.7±15.3	121.0±14.1	135.7±16.2 [^]	122.7±16.2	135.9±16.8 [^]	129.9±16.2	143.6±18.3
Diastolic blood pressure (mmHg)	71.7±8.8	72.2±9.0	69.9±8.1	78.8±9.5 [^]	74.2±9.1	77.3±9.9	78.3±11.6	84.7±11.1
Heart rate (b/pm)	76 (57-102)	79 (58-103)	71 (53-100)	71 (54-101)	71 (54-100)	77 (58-103)	71 (53-101)	67 (52-98)
Central systolic blood pressure (mmHg)	109.9±12.4	113.5±13.2	106.3±11.7	121.8±14.0 [°]	114.6±13.8	131.1±18.2 [°]	125.3±14.7	139.2±18.8
Central pulse pressure (mmHg)	52.8±5.8	53.5±5.9	51.1±5.3	58.9±6.3 [^]	48.5±4.8	58.6±6.3 [°]	51.6±5.5	58.8±6.4
Augmentation index (%)	6.8±1.7	14.0±3.5 [^]	6.4±1.4	24.3±5.2 [*]	19.3±4.4	24.6±5.4	27.6±6.2	27.8±6.5

Pulse wave velocity (m/s)	7.1±1.5	7.5±1.7	7.1±1.6	7.7±2.0	8.3±2.1	8.1±1.9	9.7±2.8°	8.1±1.8
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results are shown as mean +/- SD or median (interquartile range)

*** - p<0.001; ° - p<0.01; ^ - p<0.05**