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ORIGINAL ARTICLE

The effects of glucocorticoid treatment on cardiovascular system in patients with systemic lupus erythematosus

Dominika Blachut, Brygida Przywara-Chowaniec, Jan Harpula, Andrzej Tomasik, Ewa Nowalany-Kozielska, Beata Morawiec

2nd Department of Cardiology, Medical University of Silesia in Katowice, Zabrze, Poland

ABSTRACT

Objectives: This study aims to assess variables concerning arterial stiffness including carotid-femoral pulse wave velocity, carotid-radial pulse wave velocity, ankle-brachial index, and the advancement of atherosclerosis development.

Patients and methods: Between October 2016 and December 2020, a total of 43 consecutive patients with systemic lupus erythematosus (SLE) (4 males, 39 females; mean age: 57±8 years; range, 42 to 65 years) were prospectively included in the study. All data were compared between the group treated with glucocorticoids and that not treated with these agents.

Results: The study group consisted of 43 patients with SLE, while 22 (51%) patients were treated with glucocorticoids. The mean duration of SLE was 12.3±5.3 years. Patients treated with glucocorticoids had lower values of ankle-brachial index compared to those who were not treated with glucocorticoids (p=0.041), although the values were within the range. A similar situation was reported for the carotid-femoral artery pulse wave velocity (p=0.032). However, carotid-radial artery pulse wave velocity was not significantly different between both groups (p=0.12).

Conclusion: Properly selected therapy is important in the prevention of CVD.

Keywords: Ankle-brachial index, carotid intima-media thickness, heart disease risk factors, Systemic lupus erythematosus, vascular stiffness.

Systemic lupus erythematosus (SLE) is a rare autoimmune disease of which occurrence varies depending on the geographical location, with the highest ratio in the North America and lowest in Europe and Africa.[1,2] Since 1999, the mortality of SLE has been decreasing. However, the risk of death is still approximately three times higher compared to healthy individuals. The most common causes of death in patients include renal impairment (lupus nephritis), infections, and cardiovascular complications, which results in a shorter life expectancy, although the treatment for SLE is improved.[3-5]

One of the reasons is related to the nature of SLE, since not only common cardiovascular risk factors are involved, but also those emerging from the disease itself. As SLE develops, the autoimmune response results in inflammation, which is linked to an increased secretion of cytokines, chemokines, and autoantibodies. These molecules can affect the endothelium, leading to accelerated atherogenesis and oxidative stress.[6,7]

Methods used to assess atherogenic lesions include carotid intima-media thickness (cIMT), which is increased in SLE[8] and pulse wave velocity (PWV) measured between the carotid-femoral and

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Correspondence: Dominika Blachut, MD. 2nd Department of Cardiology, Specialist Hospital in Zabrze, 10 M. Curie-Skłodowskiej street, 41-800 Zabrze, Poland.
Tel: +48510137212 e-mail: dominikadyrcz@gmail.com

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carotid radial arteries, which provides information about arterial stiffness in the larger area than cIMT. There are, however, contrary data showing how SLE affects PWV values.[9-11]

Arterial stiffness, itself, can be altered by a series of variables, including age, arterial hypertension, dyslipidemia, metabolic disorder, or inflammatory process. Next to classical cardiovascular risk factors, the activity of SLE and chronic systemic inflammation modify vascular lesion progression.[6,12-15] Moreover, long-term glucocorticoid (GC) treatment may have various effects on the cardiovascular system in SLE patients.[16] There are findings supporting the opinion that the effect of GC is dose dependent-low doses may have an anti-atherogenic effect, yet higher doses could accelerate the development of atherosclerotic lesions.[17] The European League Against Rheumatism (EULAR) guidelines recommend that GC therapy should be used with the lowest effective dose. Probably, the assessment of the arterial stiffness in GC-treated SLE patients may allow the assessment of the anti-atherosclerosis effect and may give insight into better therapy planning.[18-20]

In the present study, we aimed to assess the variables related to arterial stiffness, such as carotid-femoral PWV (cfPWV), carotid-radial PWV (crPWV), ankle-brachial index (ABI), and the assessment of atherosclerosis and cIMT in patients with SLE and to assess the effect of GC treatment on these variables.

PATIENTS AND METHODS

This study was conducted at Medical University of Silesia in Katowice, Poland, Department of Cardiology between October 2016 and December 2020. A total of 43 consecutive patients with SLE (4 males, 39 females; mean age: 57±8 years; range, 42 to 65 years) were prospectively enrolled in the study. The diagnosis of SLE was confirmed based on the Systemic Lupus International Collaborating Clinics criteria (SLICC) and validated by the Department of Dermatology. Patients with other connective tissue diseases or overlapping connective tissue diseases, chronic inflammation related to other factors, cancerous diseases and pregnant women were excluded from this study. The activity of the disease was measured by the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K), with the cut-off point at 6 points for active disease. The score of 0 indicated remission. Only patients aged over 18 years were included. However, patients with significant cardiovascular diseases (CVDs) were excluded from the study. Both patient groups were marked by similar risk factors such as age, sex, overweight, obesity, smoking, lipid disorders, and family history.

Baseline clinical data and cardiovascular risk factors were collected. Each patient underwent the assessment of cIMT, ABI, PWV, lipid profile, and creatine. All data were compared between the group treated with GC and that not treated with these agents. The correlation between GC treatment and the development of cardiovascular risk factors was assessed. All measurements were taken during a routine examination by the professional medical staff.

The assessment of cIMT was performed with the ultrasonographic device (GE Healthcare Vivid 7; linear 10 MHz probe). Both left and right carotid arteries were assessed with the patient lying supine (head tilted to the contralateral side). The measurements were performed in a projection parallel to the vessel, 1 to 2 cm below the carotid artery bifurcation, as described in the protocol of the American Society of Echocardiography (ASECHO).[21] The values were presented in mm.[22,23]

The PWV measurement was carried out using the Complior Analyse system (Alam Medical, Saint-Quentin-Fallavier, French) and the software, according to the manufacturer's instructions. Patients fasted, did not smoke tobacco, nor did they exercise for 12 h before the assessment. The examination was performed in a neutral temperature (22 to 24°C) in a quiet room. Firstly, the blood pressure was measured three times on both upper limbs by the Microlife WatchBP Office (Microlife® WatchBP®; Microlife AG Swiss Corp., Widnau, Switzerland) and the distance between the carotid-femoral and carotid radial arteries was measured. Next, the sensors were attached to the dedicated areas (carotid, femoral, and radial arteries) and, when the quality of signal was above 90%, the measurement was considered successful.

The ABI measurement was taken after assessment of blood pressure using Microlife WatchBP Office. The patient was in a supine position, cuffs were placed around the patient's upper limb and the lower limb above the ankle. The test was repeated for both the right and left ankles, with the cuffs attached.[24,25]

Statistical analysis

Statistical analysis was performed using the Statistica version 13.3 (StatSoft Inc., Tulsa, OK, USA). Descriptive data were presented in mean ± standard deviation (SD), median (min-max) or number and frequency, where applicable. Distribution type of the selected parameters was tested using the Shapiro-Wilk test. The Student t-test was used for data with normal distribution, whereas the Mann-Whitney U test was used for non-parametric data. Unpaired Student t-test and analysis of variance (ANOVA) test were used to compare the mean values. Independence of categorical variables was assessed using the chi-square test. The assessment of the correlation factor for quantitative values was conducted using the Pearson correlation test (for normal distribution) and the Spearman test (for non-parametric data). A p value of <0.05 was considered statistically significant.

RESULTS

Of the patients, 22 (51.16%) were treated with GC. In the study group, nine patients were active tobacco users. The mean disease duration was 12.3±5.3 years, while the mean duration of treatment with GC was 9.6±4.9 years. According to the SLEDAI-2K, the activity of the SLE showed a mean of 6.4±5.8 points, with 18 (41.86%) patients above 6 points, 12 (27.91%) in complete remission and 13 (30.23%) with low disease activity. In the study group, 22 (51.16%) patients

Table 1. Baseline characteristics of the patient groups

	Study group (n=43)			Treated with GCS (n=22)			Without drugs/others (n=21)		
	n	%	Mean±SD	n	%	Mean±SD	n	%	Mean±SD
Female	39					18	12		
Age (year)			57.4±8.5			58.3±8.2			56.4±8.8
Disease duration (year)			12.3±5.3			14.9±4.8			9.3±4.1
BMI (kg/m^2)			24.8±2.8			24.6±3.5			25.0±1.9
GCS	22			22			0		
Obesity	3			3			0		
Creatinine (mg/dL)			72.3±10.8			72.4±12.2			72.2±7.8
Smoking		9		9				0	
SLEDAI-2K [pts]			6.4±5.8			6.7±5.7			6.0±5.8
Lipid profile									
Total cholesterol (mg/dL)			208.2±31.9			216.1±27.5			200.3±34.0
High density cholesterol (mg/dL)			61.0±16.9			63.7± 20.6			57.8±10.0
Low density cholesterol (mg/dL)			125.6±35.7			135.7±34.4			115.6±34.1
Triglycerides (mg/dL)			117.1±25.4			125.8±23.4			108.3±24.3
Serological									
ANAs (+)	38	88.37							
dsDNA	21	48.83							
RNP	2	4.65							
SSA/Ro	20	46.51							
SSB/La	3	9.30							
Anti-Smith antibodies	8	18.60							

GCS: Corticosteroids; SD: Standard deviation; BMI: Body Mass Index; SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index 2000; ANAs: Antinuclear antibodies; dsDNA: Anti-double-strand DNA antibodies; RNP: Anti-ribonucleoprotein antibodies; SSA/Ro: Anti-Ro antibodies; SSB/La: Anti-La antibodies.

Table 2. Studied parameters

	Whole population (n=43)	Group 1 GCS (n=22)	Group 2 Without drugs/other (n=21)	
	Mean±SD	Mean±SD	Mean±SD	*p*
IMTc (mm)	1.3±0.5	1.5±0.3	1.1±0.2	**0.0006**
ABI right ankle	1.2±0.1	1.1±0.1	1.3±0.1	**0.0479**
ABI left ankle	1.2±0.1	1.2±0.1	1.24±0.1	**0.0411**
PWV CF (m/s)	8.4±1.3	8.0±1.2	8.8±1.2	**0.0324**
PWV CR (m/s)	9.3±1.5	8.9±1.2	9.7±1.7	0.1158
Peripheral BP systolic	132.7±10.6	126.4±7.5	139.0±9.4	**0.0001**
Peripheral BP diastolic	79.4±6.8	76.6±4.5	82.3±7.5	**0.0132**
Central BP systolic	116.3±30.6	118.0±8.7	114.6±42.5	0.1445
Central BP diastolic	79.4±6.8	76.6±4.5	82.3±7.5	**0.0132**
MAP (mmHg)	90.6±21.8	93.0±4.6	88.1±30.3	0.4827
PP ratio	1.2±11.0	1.2±7.4	1.2±12.8	0.7436
Alx (%)	24.8±10.1	28.6±13.8	22.1±6.4	0.2943

GCS: Corticosteroid; SD: Standard deviation; IMTc: Intima-media complex thickness; ABI: Ankle-brachial index; PWV CF: Carotid-femoral pulse wave velocity; PWV CR: Carotid radial pulse wave velocity; BP: Blood pressure; MAP: Mean arterial pressure; PP ratio: pulse pressure ratio; Alx: Augmentation index.

were on oral GC with the doses below 7.5 mg/d. Fifteen (34.89%) patients were not treated and six (13.95%) were on chloroquine. On the basis of the above, two groups were formed; i.e., the one on GC and the one with patients on therapy other than GC or those who did not undergo any therapy.

The mean overall BMI was 24.8±2.8 kg/m^2, but the difference between the groups was not statistically significant (24.6±3.5 *vs.* 24.9±1.9 kg/m^2, p=0.7157). The percentages of abnormal values (>25 kg/m^2) were 15% and 11%, respectively (p=0.6885). Differences in creatine concentrations were not significant between the

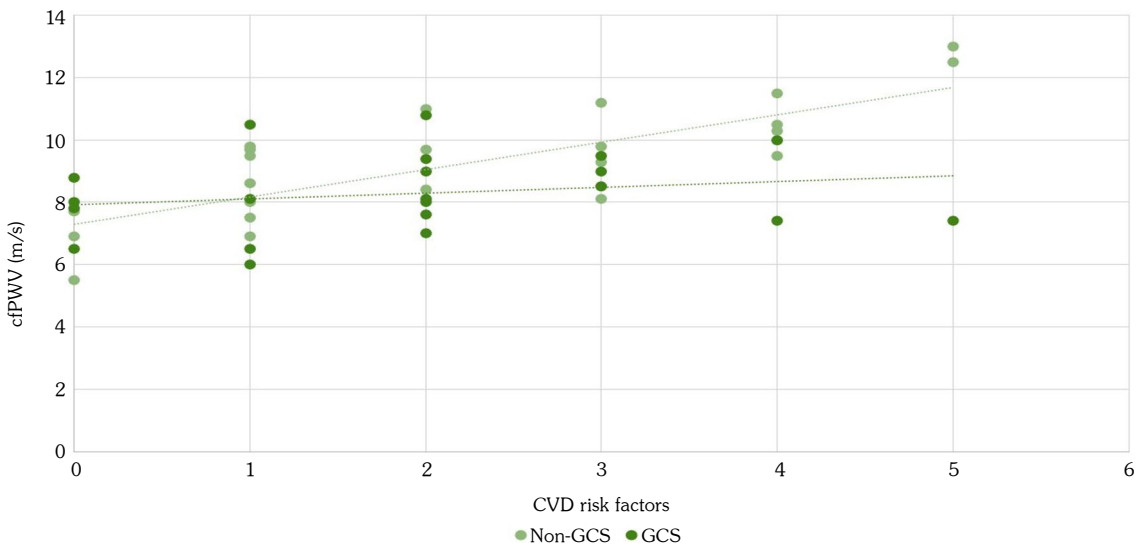

Figure 1. Correlation with CVS risk factors with cfPWV in study group.
CVD: Cardiovascular diseases; GCS: Corticosteroids; cfPWV: Carotid-femoral pulse wave velocity.

groups. Baseline characteristics of the patient groups are given in Table 1.

The analysis of the parameters showed that ABI was within the normal range. However, it was significantly lower in the GC group (right ankle 1.13 *vs.* 1.26, p=0.0473; left ankle 1.18 *vs.* 1.24, p=0.0413). Peripheral blood pressure was higher in the GC group (systolic 126 *vs.* 139 mmHg, p=0.0001; diastolic 76 *vs.* 82 mmHg, p=0.0125). The cfPWV was higher in the group with no GC therapy (8.00 *vs.* 8.83 m/s, p=0.0319), as in the case of crPWV. However, it did not show a statistically significant difference (8.89 *vs.* 9.61 m/s, p=0.1159). The cIMT values were significantly higher in the GC group (1.51 *vs.* 1.13 mm, p=0.0006). The augmentation index (AIx) was not statistically significant (28.56 *vs.* 22.05, respectively; p=0.2943). The correlation between the concentration of creatine and PWV was not statistically significant (p=0.1706). The results are given in Table 2.

New-onset CVD occurred in six (33%) patients on GC and in three (25%) patients who were not treated with GC (p=0.255). A statistically significant correlation with cardiovascular risk factors was found for cfPWV (r=0.712, p=0.021). The results are given in Figure 1.

DISCUSSION

The assessment of subclinical atherosclerosis is one of the targets for faster diagnosis of cardiovascular. Pulse wave velocity is a method that indirectly represents arterial stiffness of the central arterial region, and the data have shown that arterial stiffness is correlated with cardiovascular events and that PWV can be recognized as an independent cardiovascular risk factor.[26-28] According to some reports, arterial stiffness is correlated with left ventricular hypertrophy and chronic kidney disease.[29-32] In this study the AIx was elevated in the whole group (approximately above 10%). Therefore, AIx is not an independent risk factor, as it depends on PWV, age, sex, heart rate, blood pressure or smoking.[33]

However, the GC treatment may have various impacts on the parameters and, since steroids have been used in treatment of SLE as one of the major therapeutic options for more than 40 years, this aspect seems to be crucial for the analysis. Medium doses of GC (>7.5 mg/d) may increase the mortality rate due to chronic organ failure and may increase the number of adverse events, including cataract, osteoporosis, coronary artery disease. On the other hand, GC therapy is characterized by an anti-inflammatory effect, which may postpone the development of atherosclerotic plaques. This effect can be linked to non-genomic activity by a direct reaction with the cell membranes or by the membrane receptors. The studies mostly report the effects of GC on animals, particularly mice. However, there is no report regarding GC treatment effect in patients with SLE in the literature. Despite the increasing knowledge about the precise mechanism of action, therapy with GC in SLE still remains more art than science.[31-35]

An important aspect of this study was the assessment of arterial stiffness and the effect of GC in SLE patients. We showed that patients on GC had less elastic arteries than those who were not on GC, which could be explained by the low doses (below 7.5 mg/d) responsible for an anti-atherogenic effect. Our study also showed that patients on GC had lower cfPWV and ABI compared to the patients on therapy other than GC or those who did not undergo any treatment.

In a large number of studies, only cfPWV is tested. According to the guidelines of the European Society of Cardiology (ESC), cfPWV above 10 m/s is associated with organ damage. The guidelines, however, do not state crPWV as a useful marker of vessel impairment. In our case, crPWV results were similar to cfPWV. However, the difference was not statistically significant. It could be expected that the differences between these two parameters arise from the vessel structure. The radial artery is a muscular vessel, which in regard to the PWV is linked to the high volatility of the values, compared to the elastic type of arteries, as it is in cfPWV. Moreover, cfPWV showed a stronger correlation with cardiovascular risk factors than crPWV.[33] This study was conducted among young and healthy individuals, but there is a lack of data on the differences of PWV in SLE patients, particularly those treated with GC and other drugs. Moreover, the effect of anti-malarial drugs on arterial stiffness in the human body is not obvious, as they protect from endothelial

dysfunction in a mouse model study.[36,37] On the other hand, immunomodulation therapy, using mofetil, mycophenolate, or rituximab, may have a protective effect on the endothelium.[38,39] However, the majority of studies reported in this paper were not related to the effect of SLE treatment on vessel functioning.

It can be assumed that treatment at the early stage of SLE can prevent further complications of vascular inflammation and reverse endothelial lesions. This aspect is essential, when we analyze reports where young patients with SLE did not have significant differences in PWV compared to their healthy peers.[11,40,41]

A meta-analysis including 49 studies was related to arterial stiffness and endothelial disfunction in SLE patients and included central PWV, cfPWV, peripheral PWV and brachial-ankle PWV.[41] In total, there were 943 patients with SLE and 644 healthy individuals (control). However, the study population ranged from 5 to 220 patients in the SLE group (mean: 20 subjects). While SLE is still a rare disease, it is problematic to collect a large homogeneous group of patients, which implicates low representativeness of the study. The analysis showed that patients with SLE had higher cfPWV values indicating arterial stiffening. In our study, we examined the difference between cfPWV in various approaches to the treatment of SLE and the GC group showed significantly lower values compared to patients who were not on GC. However, in other studies, the renal factor, which is an important aspect in SLE, was not discussed. Chronic kidney disease is correlated with PWV in healthy individuals. In this study, the relationship between creatinine levels and PWV was not found. It is relevant while considering further SLE progression, as it can independently affect vascular changes.[5,32]

Sacre et al.[42] confirmed that, even in a low-risk group of CVD, arterial stiffness values were higher in SLE compared to the control group. In their study, cfPWV values were higher in the SLE group and correlated with the cIMT and the authors proposed the hypothesis that elevated systolic blood pressure and GC therapy were the main triggering factors. Barsalou et al.[43] also reported that 149 patients with childhood-onset SLE had normal cIMT, flow-mediated dilation (FMD) and PWV compared to their healthy peers. can be concluded that endothelial dysfunction develops with disease duration.

Another study suggested a correlation of arterial stiffness with atherosclerosis in the carotid artery and of arterial stiffness with elevated cIMT.[29,40,44-46] Moreover, several papers assessed the relationship of PWV with the CVD risk-higher PWV values were more likely to coexist with the risk. However, these studies were conducted on small cohorts (e.g., 50 patients with SLE). Parameters such as BMI, serum glucose, PWV, cIMT, blood pressure, mean blood pressure, aortic AIx and endothelium-dependent FMD are also evaluated. A close relationship between dyslipidemia and PWV result and CVD risk factors is suggested. The results may be related to subclinical atherosclerosis in SLE. Vascular changes were not found in young patients with SLE and those with low disease activity. The cIMT is a response to changes in blood flow and vascular stiffness.[29,40,44-46]

Morreale et al.[11] conducted a study on 50 patients with SLE and reported that cfPWV and cIMT were significantly higher in the SLE group. However, the values obtained from automatic blood pressure monitoring were higher in the group with arterial hypertension. It was suggested that the risk of premature vascular aging was similar in SLE and arterial hypertension.

Patients with active SLE may have elevated cIMT due to inflammation and reactions in the vascular wall, not only due to atherosclerosis. Therefore, it can be useful to assess not only PWV and cIMT, but also C-reactive protein and erythrocyte sedimentation rate.[46]

In the SLE vascular investigation cohort (SLEVIC), 77 patients with SLE were followed for seven years and the following conclusions were made: cIMT was similar between high and low disease activity, and GC and inflammation were the two major factors responsible for the development of cIMT. Inflammation was related to the dose of GC. The classical cardiovascular risk factors had a significant effect on vascular changes. However, the number of cardiovascular events was higher in the SLE compared to the group without SLE.[47] As a result, adequate

treatment can halt the development of vascular impairment. It is crucial that management of other chronic diseases, such as arterial hypertension or dyslipidemia, may play a role in lowering cIMT values.

Of note, the measurement of cIMT is only restricted to the small region of the whole vascular system-approximately 2-cm of the carotid artery is under assessment. On the other hand, the estimation of PWV is related to the assessment of the central (cfPWV) and peripheral (crPWV) circulation. This variable could be a reason why these values in our study were not the same.[48]

A large number of reports included different autoimmune or connective tissue diseases. The findings showed that PWV was higher compared to the control. However, one of the limitations of such studies is that these diseases have a heterogeneous course. The common factors include inflammation and accelerated aging, which are both risk factors for cardiovascular disease.[9,49-51] For instance, in the study including the antiphospholipid syndrome, systemic sclerosis, and rheumatoid arthritis, patients affected with these diseases had significantly higher cIMT and PWV (measured with the TensioClinic arteriograph) than the control group.[26] Furthermore, a strong correlation was reported between PWV and cIMT, and between these values and age. Elevated PWV may be linked to endothelial dysfunction and atherosclerosis in patients with autoimmune diseases.[26]

An important limitation of our study is the size of the study group and its cross-sectional characteristics. Poland is a country with a low morbidity of SLE. However, we were able to collect an adequate number of patients to conduct the preliminary study. As the outcomes showed, a low dose of GC could have a significant impact on the risk of CVD in SLE. The assessment presented here is low-cost and relatively easy to perform, particularly compared to the treatment of CVD and its long-term complications. The essential aspect of SLE management should be striving for remission and adequate blood pressure values, as well as general prevention of CVD. Moreover, the risk of CVD in SLE patients is assessed with standard scales. However, they do not include autoimmune diseases, which could have a great impact on further management. This could be another premise to use PWV assessment, as it has a significant predictive value, when CVD algorithms, such as Systematic Coronary Risk Estimation (SCORE) are employed.[25]

In conclusion, properly selected therapy is important in the prevention of CVD. Further studies to establish the prognostic value of PWV in SLE patients are warranted, as it could be superior to cIMT measures at the early stage of vascular impairment. Nevertheless, measurements of arterial stiffness and cIMT are a repeatable and non-invasive method to estimate a risk of CVD. Accumulated data could be the basis for further studies regarding vascular impairment and endothelial dysfunction in SLE population. Moreover, prospective research is essential to estimate the predictive value of cIMT and PWV in the CVD risk.

Ethics Committee Approval: The study protocol was approved by the Medical University of Silesia Bioethics Committee (No: KNW/0022/KB1/111/17). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Conceptualization: D.B., B.P-C., and B.M.; methodology: D.B., J.H.; software: J.H.; formal analysis: B.M.; writing-original draft preparation: D.B., J.H., B.P-C., and B.M.; writing-review and editing: E.N-K., A.T., and B.M.; visualization: D.B.; supervision: B.M. All authors have read and agreed to the published version of the manuscript.

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